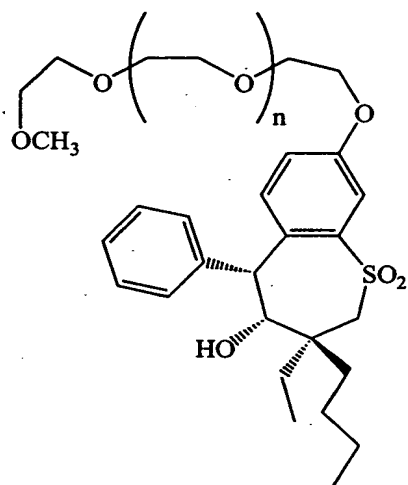


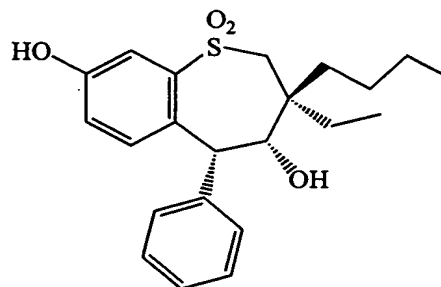
and the mixture was stirred at 60°C for an additional 2 h. The reaction mixture was triturated with 100 ml of water and extracted methylene chloride. The methylene chloride water mixture was filtered through Celite and the methylene chloride layer was dried over $MgSO_4$ and concentrated in vacuo. The first fraction (0.1 g) was compound 90, mp 117-121 °C. The second fraction (0.16 g) was compound 91, mp 68-76 °C.

[834] Example 50

[835] **A. Preparation of polyethyleneglycol functionalized benzothiepine**



No. 141



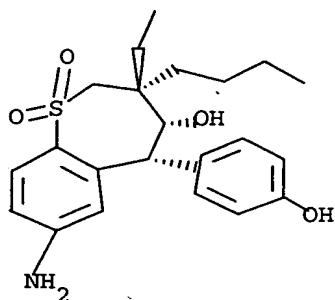
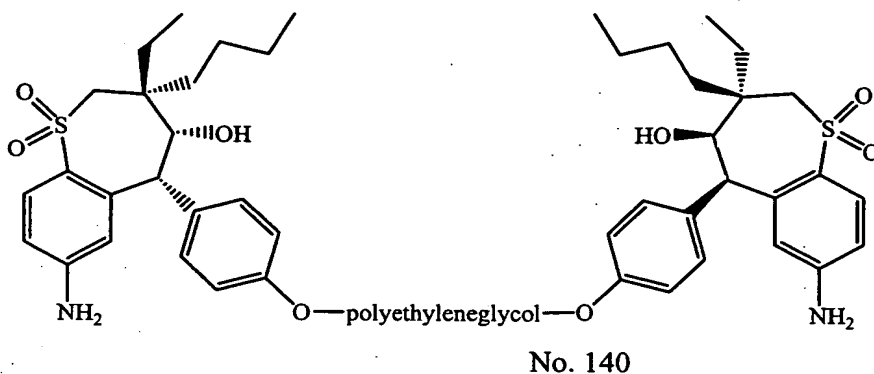
No. 136

[836] A 50 ml rb flash under a nitrogen atmosphere was charged with 0.54 g of M-Tres-5000 (Polyethyleneglycol Tresylate [methoxy-PEG-Tres, MW 5000] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.055 g Compound No. 136, 0.326 C_5CO_3 and 2cc anhydrous acetonitrile. The reaction was stirred at 30°C for 5 days and then the solution was filtered to remove salts. Next, the acetonitrile was removed under vacuum and the product was dissolved in THF and then precipitated by addition of hexane. The polymer precipitate was isolate by filtration from the solvent mixture (THF/hexane). This precipitation procedure was continued until no Compound No. 136 was detected in the precipitated product (by TLC SiO_2). Next, the polymer precipitate was dissolved in water and filtered and the water soluble polymer was dialyzed for 48 hours through a cellulose dialysis tube (Spectrum® 7

,45 mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried. The NMR was consistent with the desired product A and gel permeation chromatography indicated the presence of a 4500 MW polymer and also verified that no free Compound No. 136 was present. This material was active in the IBAT in vitro cell assay.

[837] Example 51

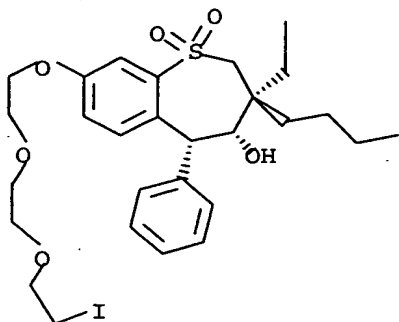
[838] **Preparation of Compound 140**



[839] Compound 140 is prepared as noted below. A 2-necked 50 ml round bottom Flask was charged with 0.42g of Tres-3400 (Polyethyleneglycol Tresylate [Tres-PEG-Tres,MW 3400] purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), 0.1 potassium carbonate, 0.100g of Compound No. 111 and 5 ml anhydrous DMF. Stir for 6 days at 27 °C. TLC indicated the disappearance of the starting Compound No. 111. The solution was transferred to a separatory funnel and diluted with 50 cc methylene chloride and

then extracted with water. The organic layer was evaporated to dryness by means of a rotary evaporator. Dry wgt. 0.4875 g. Next, the polymer was dissolved in water and then dialyzed for 48 hours at 40°C through a cellulose dialysis tube (spectrum® 7, 45mm x 0.5 ft, cutoff 1,000 MW). The polymer solution was then removed from the dialysis tube and lyophilized until dried (0.341 g). NMR was consistent with the desired product 140.

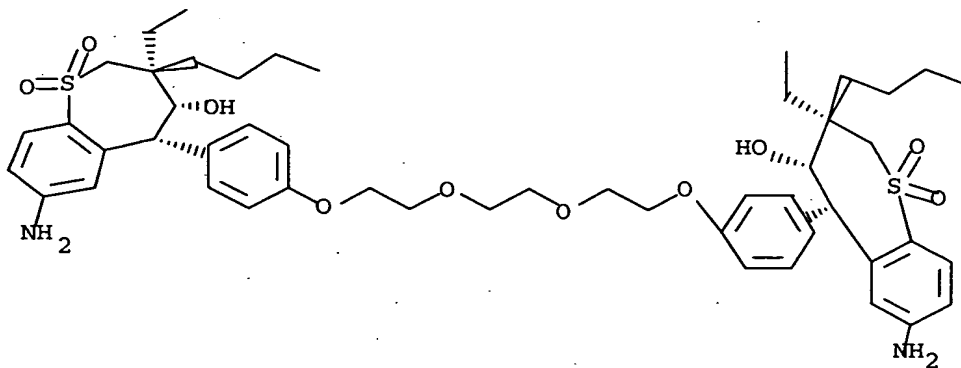
[840] Example 52



No. 134

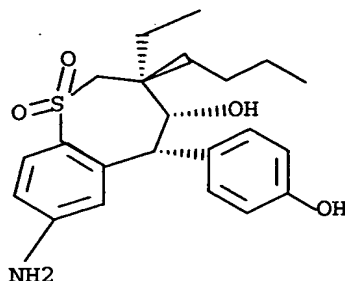
[841] A 10 cc vial was charged with 0.21 g of Compound No. 136 (0.5mmoles), 0.17g (1.3 mmoles)potassium carbonate, 0.6g (1.5 mmoles) of 1,2-bis-(2-iodoethoxy)-ethane and 10 cc DMF. The reaction was stirred for 4 days at room temperature and then worked up by washing with ether/water. The ether layer was stripped to dryness and the desired product Compound No. 134 was isolated on a silica gel column using 80/20 hexane ethyl acetate.

[842] Example 53



No. 112

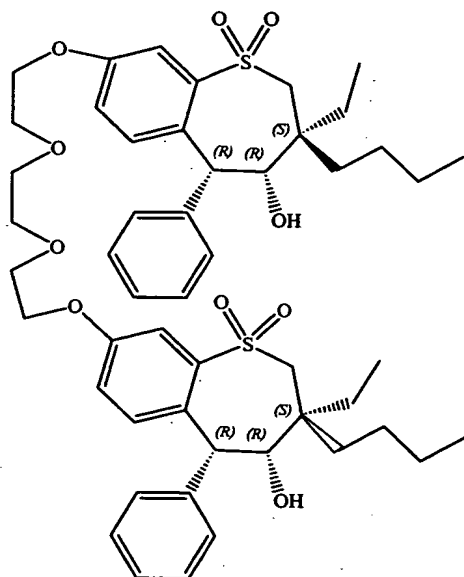
[843] Example 54



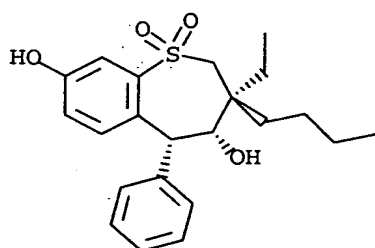
No. 113

[844] Preparation of compound no. 112 is described below. A two necked 25 ml round bottom Flask was charged with 0.5g (1.24mmoles) of compound no. 134, *infra*, 13 mls of anhydrous DMF, 0.055g of 60% NaH dispersion and 0.230g (0.62 mmoles) of 1,2-Bis [2-iodoethoxyethane] at 10°C under nitrogen. Next, the reaction was slowly heated to 40 °C. After 14 hours all of the Compound No. 113 was consumed and the reaction was cooled to room temperature and extracted with ether/water. The ether layer was evaporated to dryness and then chromatographed on Silicage (80/20 ethyl acetate/hexane). Isolated Compound No. 112 (0.28 g) was characterized by NMR and mass spec.

[845] Example 55



No. 135



No. 136

[846] Preparation of compound no. 135 is described below. In a 50 ml round bottom Flask, add 0.7g (1.8 mmoles) of Compound No. 136, 0.621g of potassium carbonate, 6 ml DMF, and 0.33g of 1,2-Bis [2-iodoethoxyethane]. Stir at 40°C under nitrogen for 12 hours. The workup and isolation was the same procedure for Compound No. 112.

[847] Examples 56 and 57 (Compound Nos. 131 and 137)

[848] The compositions of these compounds are shown in Table 3, *infra*.

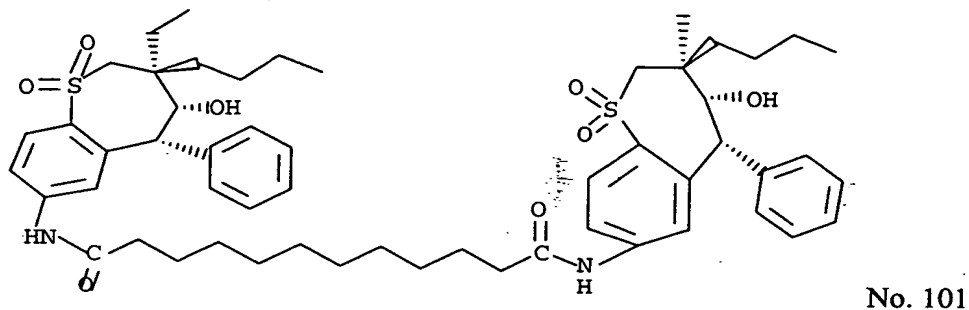
[849] The same procedure as for Example 55 except appropriate benzothiepine was used.

[850] Example 58 (Compound No. 139)

[851] The composition of this compound is shown in Table 3 *infra*.

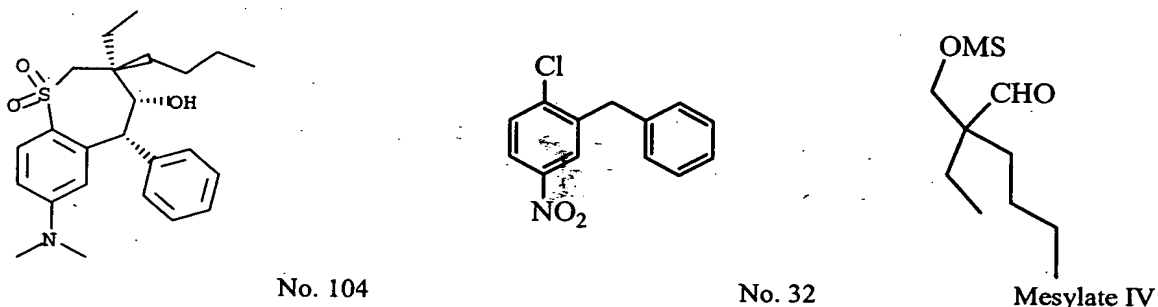
[852] Same procedure as for Example 55 with appropriate benzothiepine 1,6 diiodohexane was used instead of 1,2-Bis [2-iodoethoxyethane].

[853] Example 59 (Compound No. 101)



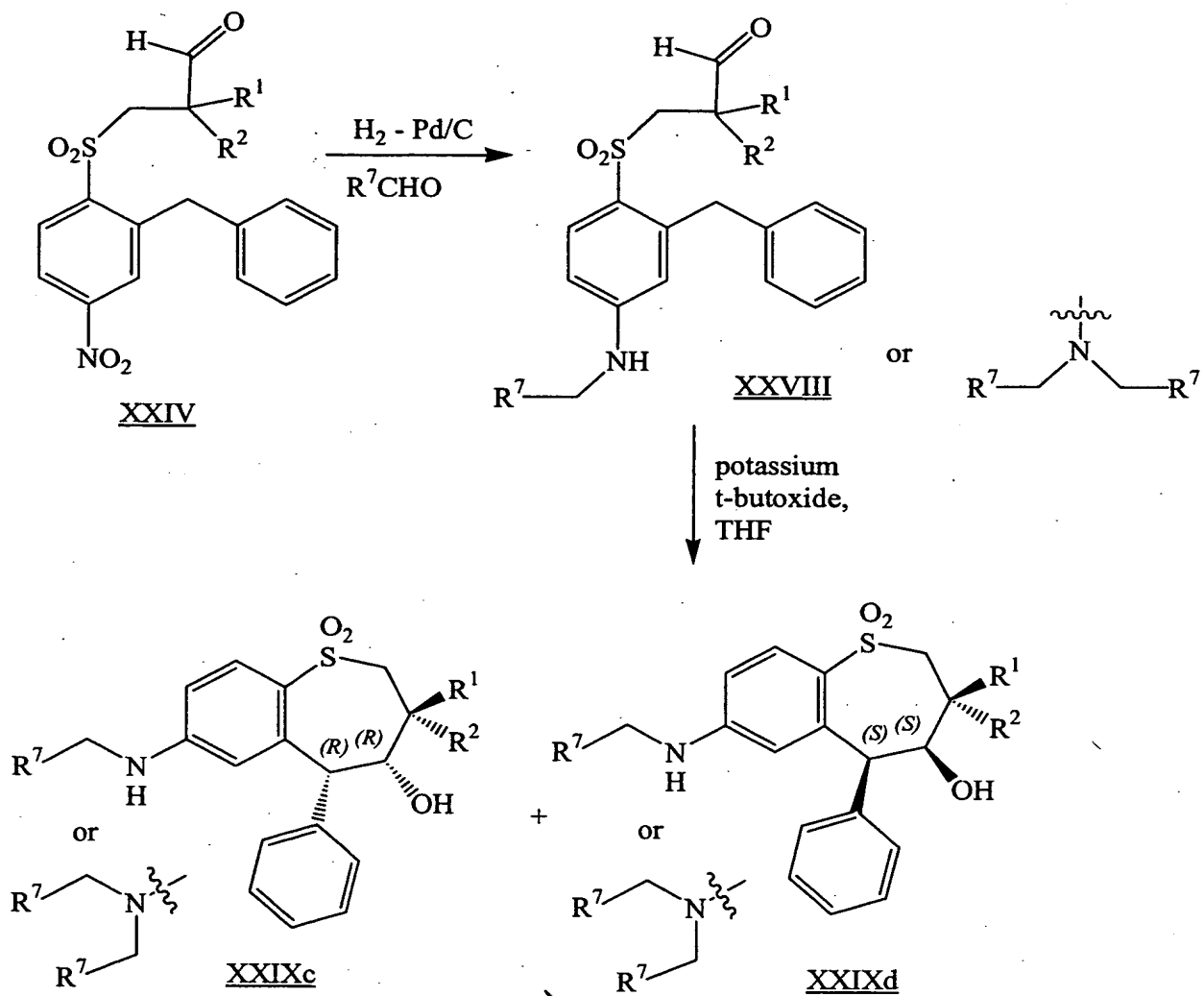
[854] This compound is prepared by condensing the 7-NH₂ benzothiepine with the 1,12-dodecane dicarboxylic acid or acid halide.

[855] Example 60 (Compound No. 104)



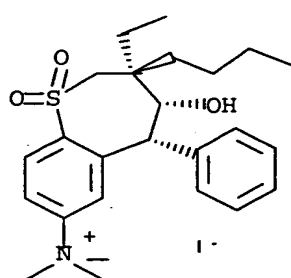
[856] 2-Chloro-5-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-5-nitrodiphenylmethane 32. Reaction of 32 (similar to S2-32 of Scheme 2, *supra*) with lithium sulfide followed by reacting the resulting sulfide with mesylate IV (similar to compound S2-33 of Scheme 2, *supra*) gives sulfide-aldehyde XXIII (similar to compound S2-34 of Scheme 2, *supra*). Oxidation of XXIII (not shown) with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 8 below). Reduction of the sulfone-aldehyde XXIV with 100 psi hydrogen and 55°C for 12 hours catalyzed by palladium on carbon in the same reaction vessel together with R'⁷CHO yields the substituted dimethylamine derivative XXVIII. Cyclization of XXVIII with potassium *t*-butoxide yields a mixture of substituted amino derivatives XXIXc and XXIXd.

[857] SCHEME 8

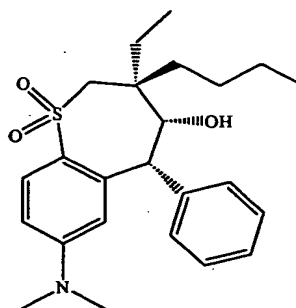


Especially for $\text{R}^7 = \text{H}$

[858] Example 61



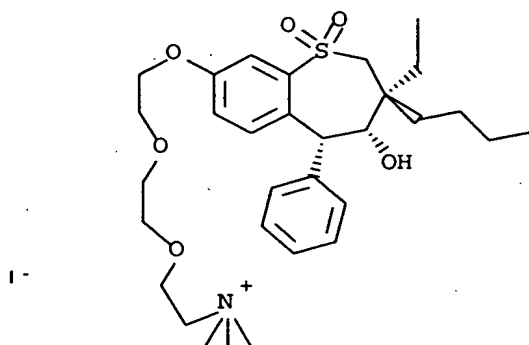
No. 102



No. 70112

[859] A 1 oz. Fisher-porter bottle was charged with 0.14 g (0.34 mmoles) of compound no. 70112, 0.97 gms (6.8 mmoles) of methyl iodide, and 7 ml of anhydrous acetonitrile. Heat to 50°C for 4 days. The quat. Salt Compound No. 192 was isolated by concentrating to 1 cc acetonitrile and then precipitating with diethyl ether.

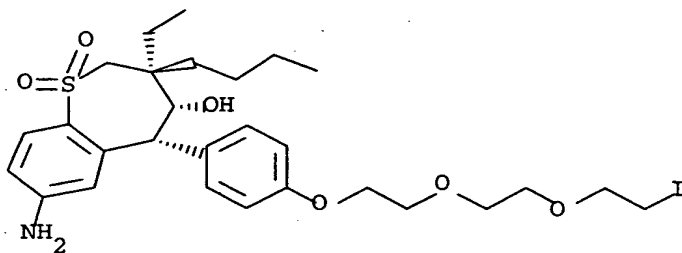
[860] Example 62



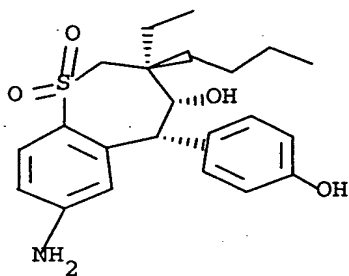
No. 125

[861] A 0.1 g (0.159 mmoles) sample of Compound No. 134 was dissolved in 15 ml of anhydrous acetonitrile in a Fischer-porter bottle and then trimethylamine was bubbled through the solution for 5 minutes at 0°C and then capped and warmed to room temperature. The reaction was stirred overnight and the desired product was isolated by removing solvent by rotary evaporation.

[862] Example 63 (Compound No. 295)



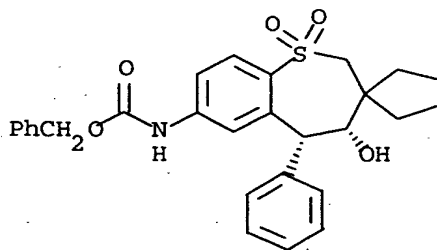
No. 295



No. 113

[863] Sodium Hydride 60% (11 mg, 0.27 mmoles) in 1 cc of acetonitrile at 0°C was reacted with 0.248 mmoles (.10 g) of Compound No. 113 in 2.5cc of acetonitrile at 0 °C. Next, 0.980g 2.48 mmoles) of 1,2-Bis [2-iodoethoxyethane]. After warming to room temperature, stir for 14 hours. The product was isolated by column chromatography.

[864] Example 64 (Compound No. 286)

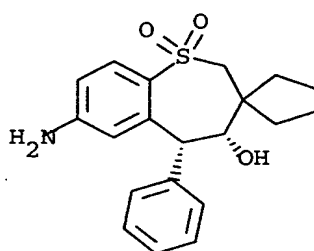


No. 286

[865] Following a procedure similar to the one described in Example 86, *infra* (see Compound No. 118, Table 3, *infra*), the title compound was prepared and purified

as a colorless solid; mp 180-181 °C; ^1H NMR (CHCl_3) δ 0.85 (t, J = 6 Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.24-1.42 (m, 2H), 1.46-1.56 (m, 1H), 1.64-1.80 (m, 1H), 2.24-2.38 (m, 1H), 3.15 (AB, J_{AB} = 15 Hz, $\Delta\nu$ = 42 Hz, 2H), 4.20 (d, J = 8 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.46 (s, 1H), 6.68 (s, 1H), 7.29-7.51 (m, 10H), 7.74 (d, J = 8 Hz, 1H), 8.06 (d, J = 8 Hz, 1H). FABMS m/z 494 ($\text{M}+\text{H}$), HRMS calcd for ($\text{M}+\text{H}$) 494.2001, found 494.1993. Anal. Calcd. for $\text{C}_{28}\text{H}_{31}\text{NO}_5\text{S}$: C, 68.13; H, 6.33; N, 2.84. Found: C, 68.19; H, 6.56; N, 2.74.

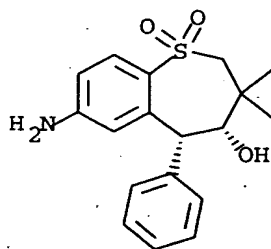
[866] Example 65 (Compound No. 287)



No. 287

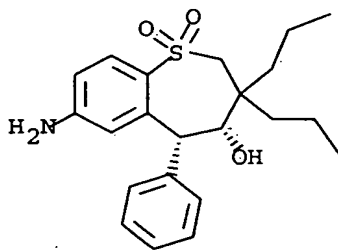
[867] Following a procedure similar to the one described in Example 89, *infra* (see Compound No. 121, Table 3, *infra*), the title compound was prepared and purified as a colorless solid: mp 245-246 °C, ^1H NMR (CDCl_3) δ 0.84 (t, J = 6 Hz, 3H), 0.92 (t, J = 6 Hz, 3H), 1.28, (d, J = 8 Hz, 1H), 1.32-1.42 (m, 1H), 1.48-1.60 (m, 1H), 1.64-1.80 (m, 1H), 2.20-2.36 (m, 1H), 3.09 (AB, J_{AB} = 15 Hz, $\Delta\nu$ = 42 Hz, 2H), 3.97 (bs, 2H), 4.15 (d, J = 8 Hz, 1H), 5.49 (s, 1H), 5.95 (s, 1H), 6.54 (d, J = 7 Hz, 1H), 7.29-7.53 (m, 5H), 7.88 (d, J = 8 Hz, 1H); ESMS 366 ($\text{M}+\text{Li}$). Anal. Calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_3\text{S}$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.54; H, 7.20; N, 3.69.

[868] Example 66 (Compound No. 288)



[869] Following a procedure similar to the one described in Example 89, *infra* (see Compound No. 121, Table 3, *infra*), the title compound was prepared and purified by silica gel chromatography to give the desired product as a colorless solid: mp 185-186°C; ^1H NMR (CDCl_3) δ 1.12 (s, 3H), 1.49 (s, 3H), 3.00 (d, $J = 15$ Hz, 1H), 3.28 (d, $J = 15$ Hz, 1H), 4.00 (s, 1H), 5.30 (s, 1H), 5.51 (s, 1H), 5.97 (s, 1H), 6.56 (dd, $J = 2.1, 8.4$ Hz, 1H), 7.31-7.52 (m, 5H), 7.89 (d, $J = 8.4$ Hz, 1H). MS (FAB+) ($\text{M}+\text{H}$) m/z 332.

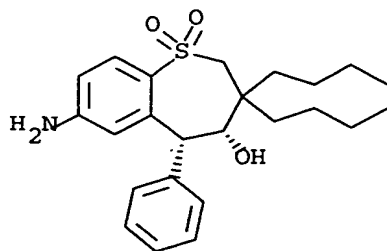
[870] Example 67 (Compound No. 289)



1No. 289

[871] Following a procedure similar to the one described in Example 89, *infra* (see Compound No. 121, Table 3, *infra*), the title compound was prepared and purified by silica gel chromatography to give the desired product as a white solid: mp 205-206 °C; ^1H NMR (CDCl_3) δ 0.80-0.95 (m, 6H), 1.10-1.70 (m, 7H), 2.15 (m, 1H), 3.02 (d, $J = 15.3$ Hz, 2H), 3.15 (d, $J = 15.1$ Hz, 2H), 3.96 (s, br, 2H), 4.14 (d, $J = 7.8$ Hz, 1H), 5.51 (s, 1H), 5.94 (d, $J = 2.2$, 1H), 6.54 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.28-7.50 (m, 6H), 7.87 (d, $J = 8.5$ Hz, 1H). MS (FAB): m/z 388 ($\text{M}+\text{H}$).

[872] Example 68 (Compound No. 290)

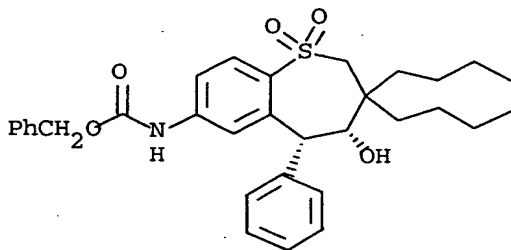


2

No. 290

[873] Following a procedure similar to the one described in Example 89, *infra* (see Compound No. 121, Table 3, *infra*), the title compound was prepared and purified as a colorless solid: mp = 96-98 °C, ^1H NMR (CDCl_3) δ 0.92 (t, J = 7 Hz, 6H), 1.03-1.70 (m, 11H), 2.21 (t, J = 8 Hz, 1H), 3.09 (AB, J_{AB} = -18 Hz, $\Delta\nu$ = 38 Hz, 2H), 3.96 (bs, 2H), 4.14 (d, J = 7 Hz, 1H), 5.51 (s, 1H), 5.94 (s, 1H), 6.56 (d, J = 9 Hz, 1H), 7.41-7.53 (m, 6H), 7.87 (d, J = 8 Hz, 1H); FABMS m/z 416 ($\text{M}+\text{H}$).

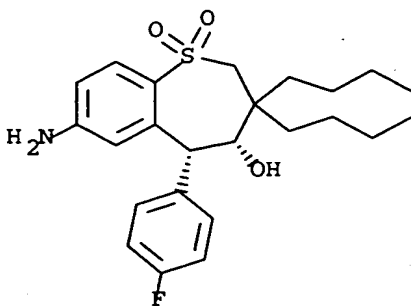
[874] Example 69



No. 291

[875] Following a procedure similar to the one described in Example 86, *infra* (see Compound No. 118, Table 3, *infra*), the title compound was prepared and purified as a colorless solid: ^1H NMR (CDCl_3) δ 0.91 (t, J = 7 Hz, 6H), 1.02-1.52 (m, 11H), 1.60-1.70 (m, 1H), 2.23 (t, J = 8 Hz, 1H), 3.12 (AB, J_{AB} = 18 Hz, $\Delta\nu$ = 36 Hz, 2H), 4.18 (d, J = 7 Hz, 1H), 5.13 (s, 2H), 5.53 (s, 1H), 6.43 (s, 1H), 6.65 (s, 1H), 7.29-7.52 (m, 10H), 7.74 (d, J = 9 Hz, 1H), 8.03 (d, J = 8 Hz, 1H); ESMS m/z 556 ($\text{M}+\text{Li}$).

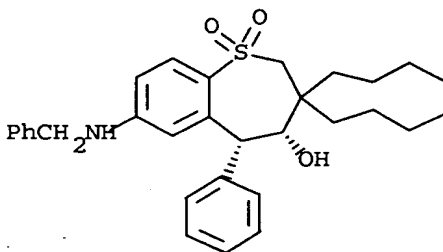
[876] Example 70 (Compound No. 292)



No. 292

[877] Following a procedure similar to the one described in Example 89, *infra* (see Compound No. 121, Table 3, *infra*), the title compound was prepared and purified as a colorless solid: mp = 111-112.5°C, ^1H NMR (CDCl_3) δ 0.90 (t, J = 8 Hz, 6H), 1.03-1.50 (m, 10H), 1.55-1.70 (m, 2H), 2.18 (t, J = 12 Hz, 2H), 3.07 (AB, J_{AB} = 15 Hz, Δv = 45 Hz, 2H), 4.09 (bs, 2H), 5.49 (s, 1H), 5.91 (s, 1H), 6.55 (d, J = 9 Hz, 1H), 7.10 (t, J = 7 Hz, 2H), 7.46 (t, J = 6 Hz, 2H), 7.87 (d, J = 9 Hz, 1H).

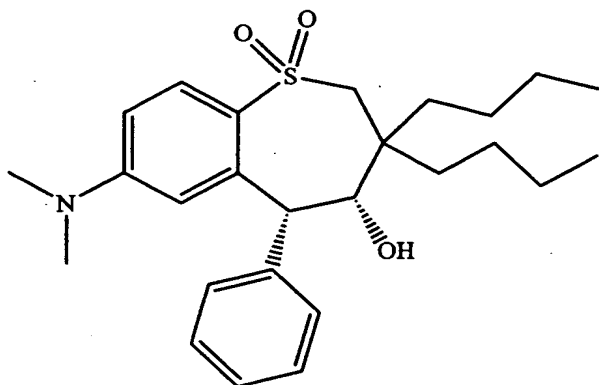
[878] Example 71 (Compound No. 293)



No. 293

[879] During the preparation of Compound No. 290 from Compound No. 291 using BBr_3 , the title compound was isolated: ^1H NMR (CDCl_3) δ 0.85 (t, J = 6 Hz, 6H), 0.98-1.60 (m, 10H), 1.50-1.66 (m, 2H), 2.16 (t, J = 8 Hz, 1H), 3.04 (AB, J_{AB} = 15 Hz, Δv = 41 Hz, 2H), 4.08 (s, 1H), 4.12 (s, 1H), 5.44 (s, 1H), 5.84 (s, 1H), 6.42 (d, J = 9 Hz, 1H), 7.12 (d, J = 8 Hz, 2H), 7.16-7.26 (m, 10H), 7.83 (d, J = 8 Hz, 1H); ESMS m/z 512 ($\text{M}+\text{Li}$).

[880] Example 72 (Compound No. 294)



No. 294

[881] Following a procedure similar to the one described in Example 60 (Compound No. 104), the title compound was prepared and purified as a colorless solid: ^1H NMR (CDCl_3) δ 0.90 (t, $J = 6$ Hz, 6H), 1.05-1.54 (m, 9H), 1.60-1.70 (m, 1H), 2.24 (t, $J = 8$ Hz, 1H), 2.80 (s, 6H), 3.05 (AB, $J_{\text{AB}} = 15$ Hz, $\Delta\nu = 42$ Hz, 2H), 4.05-4.18 (m, 2H), 5.53 (s, 1H), 5.93 (s, 1H), 6.94 (d, $J = 9$ Hz, 1H), 7.27-7.42 (m, 4H), 7.45 (d, $J = 8$ Hz, 2H), 7.87 (d, $J = 9$ Hz, 1H); ESMS m/z 444 ($\text{M}+\text{H}$).

[882] Structures of the compounds of Examples 33 to 72 are shown in Tables 3 and 3A, *infra*.

[883] Examples 73-79, 87, 88 and 91-102

[884] Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, compounds were prepared having the structures set forth in Table 3, *infra*. The starting materials illustrated in the reaction schemes shown above were varied in accordance with principles of organic synthesis well known to the art to introduce the indicated substituents in the 4- and 5- positions ($\text{R}^{4\text{A}}$, $\text{R}^{4\text{B}}$, $\text{R}^{5\text{A}}$, $\text{R}^{5\text{B}}$) and in the indicated position on the benzo ring (R^6).

[885] Structures of the the compounds produced in Examples 73-102 are set forth in Tables 3 and 3A, *infra*.

[886] Examples 80-84

[887] **Preparation of 115, 116, 111, 113**

[888] **Preparation of 4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene**

[889] In a 500 ml 2-necked rb flask weigh out 68.3 gms phosphorus pentachloride (0.328 mole 1.1 eq). Add 50 mls chlorobenzene. Slowly add 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole). Stir at room temp overnight under N₂ then heat 1 hr at 50C.

[890] Remove chlorobenzene by high vacuum. Wash residue with hexane. Dry wt=55.5 gms.

[891] In the same rb flask, dissolve acid chloride (55.5 g 0.25 mole) from above with 100 mls anisole (about 3.4 eq). Chill solution with ice bath while purging with N₂. Slowly add 40.3g aluminum chloride (1.2 eq 0.3 mole). Stir under N₂ for 24 hrs.

[892] After 24 hrs, the solution was poured into 300 mls 1N HCl soln. (cold). Stir this for 15 min. Extract several times with diethyl ether. Extract organic layer once with 2% aqueous NaOH then twice with water. Dry organic layer with MgSO₄, dry on vac line. Solid is washed well with ether and then ethanol before drying. Wt=34.57g (mixture of meta, ortho and para).

Elemental	Theory	found
C	57.65	57.45
H	3.46	5.51
N	4.8	4.8
Cl	12.15	12.16

- [893] With the next step of the reduction of the ketone with trifluoromethane sulfonic acid and triethyl silane, crystallization with ethyl acetate/hexane affords pure 4-chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene.
- [894] 4-Chloro-3-[4-methoxy-phenylmethyl]-nitrobenzene was then reacted as specified in the synthesis of 117 and 118 from 2-chloro-4-nitrophenylmethane. From these procedures 115 and 116 can be synthesized. Compounds 111 and 113 can be synthesized from the procedure used to prepare Compound 121. See Table 3, *infra*.
- [895] Compound 114 can be prepared by reaction of 116 with ethyl mercaptan and aluminum trichloride.
- [896] Examples 85 and 86
- [897] **Preparation of 117 and 118**
- [898] 2-Chloro-5-nitrobenzophenone is reduced with triethylsilane and trifluoromethane sulfonic acid to 2-chloro-5-nitrodiphenylmethane 32, *supra*. Reaction of 32 (similar to S2-32 of Scheme 2, *supra*) with lithium sulfide followed by reacting the resulting sulfide with mesylate IV (similar to compound S2-33 of Scheme 2, *supra*) gives sulfide-aldehyde XXIII (similar to compound S2-34 of Scheme 2, *supra*). Oxidation of XXIII (not shown) with 2 equivalents of MCPBA yields sulfone-aldehyde XXIV (see Scheme 8 below). Reduction of the sulfone-aldehyde XXIV with 100 psi hydrogen and 55°C for 12 hours catalyzed by palladium on carbon in the same reaction vessel together with RCHO yields the substituted dimethylamine derivative XXVIII. Cyclization of XXVIII with potassium t-butoxide yields a mixture of substituted amino derivatives XXIXc and XXIXd. See SCHEME 8, *supra*.
- [899] The sulfone-aldehyde (31.8 g) was dissolved in ethanol/toluene and placed in a parr reactor with 100 ml toluene and 100 ml of ethanol and 3.2 g of 10% Pd/C and heated to 55°C and 100 psi of hydrogen gas for 14 hours. The reaction was then filtered to remove the catalyst. The amine product (.076 moles, 29.5 g) from this reaction was then reacted with benzyl chloroformate (27.4g) in toluene in the

presence of 35 g of potassium carbonate and stirred at room temperature overnight. After work up by extraction with water, the CBZ protected amine product was further purified by precipitation from toluene/hexane.

[900] The CBZ protected amine product was then reacted with 3 equivalents of potassium t-butoxide in THF at 0°C to yield compounds 117 and 118 which were separated by silica gel column chromatography.

[901] Examples 89 and 90

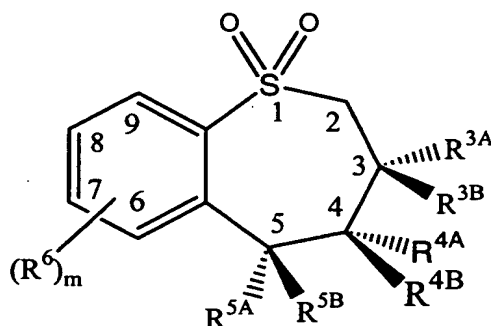
[902] **Preparation of 121 or 122**

[903] Compound 118 (.013 moles, 6.79g) is dissolved in 135 ml of dry chloroform and cooled to -78°C, next 1.85 ml of boron tribromide (4.9 g) was added and the reaction is allowed to warm to room temperature. Reaction is complete after 1.5 hours. The reaction is quenched by addition of 10% potassium carbonate at 0°C and extract with ether. Removal of ether yields Compound No. 121. See Table 3, *infra*. A similar procedure can be used to produce 122 from 117. See Table 3, *infra*.

[904] Examples 93-96

[905] Compounds 126, 127, 128 and 129 as set forth in Table 3 were prepared substantially in the manner described above for compounds 115, 116, 111 and 113, respectively, except that fluorobenzene was used as a starting material in place of anisole.

Table 3: Specific Compounds (#102-111, 113-130, 132-134, 136, 138, 142-144, 262-296)



Cp#	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}	R ^{5B}	(R ⁶) _m
102	Et-	n-Bu-	HO-	H-	Ph-	H-	I-, 7-(CH ₃) ₃ N ⁺ -
103	n-Bu-	Et-	HO-	H-	Ph-	H-	I-, 7-(CH ₃) ₃ N ⁺ -
104	Et-	n-Bu-	HO-	H-	Ph-	H-	7-(CH ₃) ₂ N-
105	Et-	n-Bu-	HO-	H-	Ph-	H-	7-CH ₃ SO ₂ NH-
106	Et-	n-Bu-	HO-	H-	Ph-	H-	7-Br-CH ₂ -CONH-
107	n-Bu-	Et-	HO-	H-	p-n-C ₁₀ H ₂₁ --O-Ph-	H-	7-NH ₂ -
108	Et-	n-Bu-	HO-	H-	Ph-	H-	7-C ₅ H ₁₁ CONH-
109	Et-	n-Bu-	HO-	H-	p-n-C ₁₀ H ₂₁ --O-Ph-	H-	7-NH ₂ -
110	Et-	n-Bu-	HO-	H-	Ph-	H-	7-CH ₃ CONH-
111	n-Bu-	Et-	HO-	H-	p-HO-Ph-	H-	7-NH ₂ -

Cp#	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}	R ^{5B}	(R ⁶) _m
113	Et-	n-Bu-	HO-	H-	p-HO-Ph-	H-	7-NH ₂ -
114	Et-	n-Bu-	HO-	H-	p-CH ₃ O-Ph-	H-	7-NH ₂ -
115	n-Bu-	Et-	HO-	H-	p-CH ₃ O-Ph-	H-	7-NH-CBZ
116	Et-	n-Bu-	HO-	H-	p-CH ₃ O-Ph-	H-	7-NH-CBZ
117	n-Bu-	Et-	HO-	H-	Ph-	H-	7-NH-CBZ
118	Et-	n-Bu-	HO-	H-	Ph-	H-	7-NH-CBZ
119	Et-	n-Bu-	HO-	H-	Ph-	H-	7-NHCO ₂ -t-Bu
120	n-Bu-	Et-	HO-	H-	Ph-	H-	7-NHCO ₂ -t-Bu
121	Et-	n-Bu-	HO-	H-	Ph-	H-	7-NH ₂ -
122	n-Bu-	Et-	HO-	H-	Ph-	H-	7-NH ₂ -
123	Et-	n-Bu-	HO-	H-	Ph-	H-	7-n-C ₆ H ₁₃ -NH-
124	n-Bu-	Et-	HO-	H-	Ph-	H-	7-n-C ₆ H ₁₃ -NH-
125	Et-	n-Bu-	HO-	H-	Ph-	H-	I ⁻ , 8-(CH ₃) ₃ N ⁺ (CH ₂ CH ₂ O) ₃ -
126	n-Bu-	Et-	HO-	H-	p-F-Ph-	H-	7-NH-CBZ
127	n-Bu-	Et-	HO-	H-	p-F-Ph-	H-	7-NH ₂ -
128	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH-CBZ
129	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH ₂ -

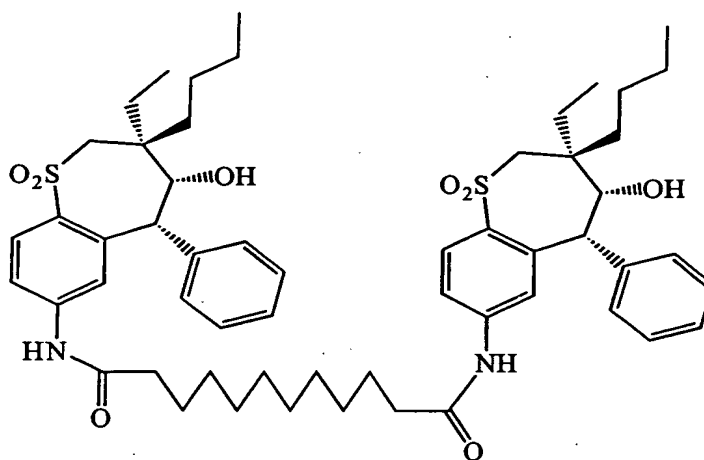
Cp#	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}	R ^{5B}	(R ⁶) _m
130	Et-	n-Bu-	HO-	H-	Ph-	H-	I-, 8- (CH ₃) ₃ N ⁺ C ₆ H ₁₂ O-
132	Et-	n-Bu-	HO-	H-	Ph-	H-	8-phthal- imidyl- C ₆ H ₁₂ O-
133	Et-	n-Bu-	HO-	H-	Ph-	H-	8-n-C ₁₀ H ₂₁ -
134	Et-	n-Bu-	HO-	H-	Ph-	H-	8- I- (C ₂ H ₄ O) ₃ -
136	Et-	n-Bu-	HO-	H-	Ph-	H-	8- HO-
138	n-Bu-	Et-	HO-	H-	Ph-	H-	8- CH ₃ CO ₂ -
142	Et-	n-Bu-	H-	HO-	H-	m-CH ₃ O-Ph-	7-CH ₃ S-
143	Et-	n-Bu-	HO-	H-	m-CH ₃ O- Ph-	H-	7-CH ₃ S-
144	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)- azetidine
262	Et-	n-Bu-	HO-	H-	m-CH ₃ O- Ph-	H-	7-CH ₃ O-
263	Et-	n-Bu-	H-	HO-	H-	m-CH ₃ O-Ph-	7-CH ₃ O-
264	Et-	n-Bu-	HO-	H-	m-CF ₃ -Ph-	H-	7-CH ₃ O-
265	Et-	n-Bu-	H-	HO-	H-	m-CF ₃ -Ph-	7-CH ₃ O-
266	Et-	n-Bu-	HO-	H-	m-HO-Ph-	H-	7-HO-

Cp#	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}	R ^{5B}	(R ⁶) _m
267	Et-	n-Bu-	HO-	H-	m-HO-Ph-	H-	7-CH ₃ O-
268	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH ₃ O-
269	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-CH ₃ O-
270	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-HO-
271	Et-	n-Bu-	HO-	H-	m-CH ₃ O-Ph-	H-	7-Br-
272	Et-	n-Bu-	H-	HO-	H-	m-CH ₃ O-Ph-	7-Br-
273	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-F-
274	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-F-
275	Et-	n-Bu-	H-	HO-	H-	m-CH ₃ O-Ph-	7-F-
276	Et-	n-Bu-	HO-	H-	m-CH ₃ O-Ph-	H-	7-F-
277	Et-	n-Bu-	HO-	H-	m-F-Ph-	H-	7-CH ₃ O-
278	Et-	n-Bu-	H-	HO-	H-	o-F-Ph-	7-CH ₃ O-
279	Et-	n-Bu-	H-	HO-	H-	m-F-Ph-	7-CH ₃ O-
280	Et-	n-Bu-	HO-	H-	o-F-Ph-	H-	7-CH ₃ O-
281	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH ₃ S-
282	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-CH ₃ -
283	Et-	n-Bu-	H-	HO-	H-	p-F-Ph-	7-CH ₃ -
284	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-morpholine
285	Et-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-(N)-pyrrolidine
286	Et-	Et-	HO-	H-	Ph-	H-	7-NH-CBZ-
287	Et-	Et-	HO-	H-	Ph-	H-	7-NH ₂ -

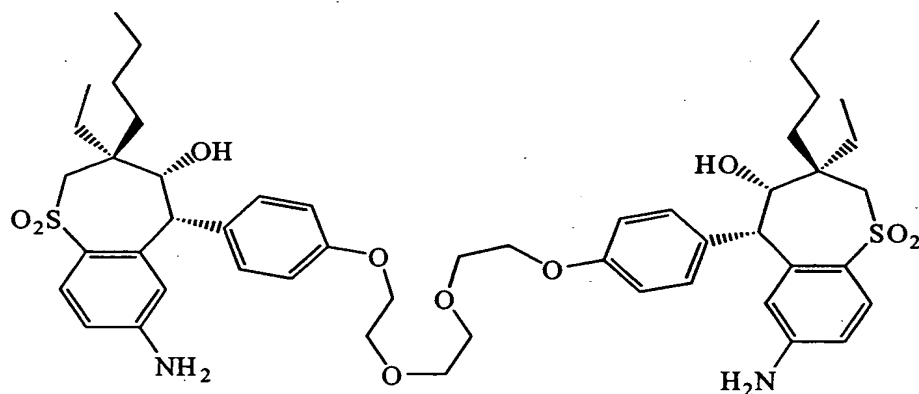
Cp#	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}	R ^{5B}	(R ⁶) _m
288	CH ₃ -	CH ₃ -	HO-	H-	Ph-	H-	7-NH ₂ -
289	n-C ₃ H ₇ -	n-C ₃ H ₇ -	HO-	H-	Ph-	H-	7-NH ₂ -
290	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-NH ₂ -
291	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-NH-CBZ-
292	n-Bu-	n-Bu-	HO-	H-	p-F-Ph-	H-	7-NH ₂ -
293	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-PhCH ₂ N-
294	n-Bu-	n-Bu-	HO-	H-	Ph-	H-	7-(CH ₃) ₂ N-
295	Et-	n-Bu-	HO-	H-	p-I-(C ₂ H ₄ O) ₃ - Ph-	H-	7-NH ₂ -
296	Et-	n-Bu-	HO-	H-	I ⁻ , p-(CH ₃) ₃ N ⁺ (C ₂ H ₄ O) ₃ - Ph-	H-	7-NH ₂ -

Table 3A

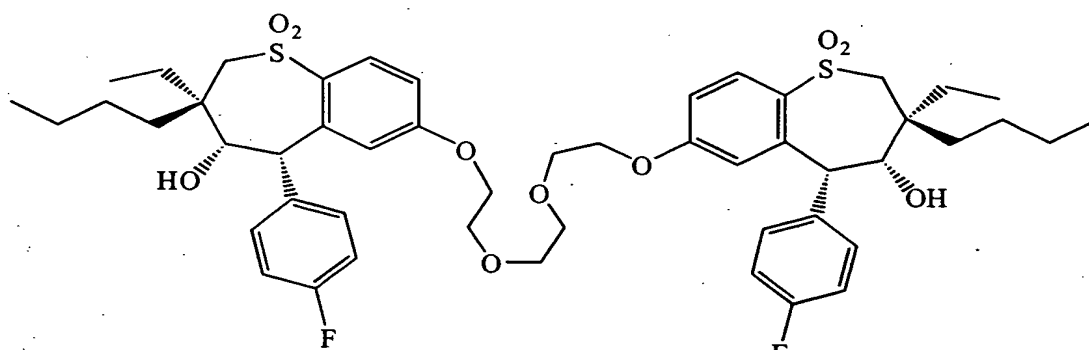
Bridged Benzothiepine (#101, 112, 131, 135, 137, 139-141)



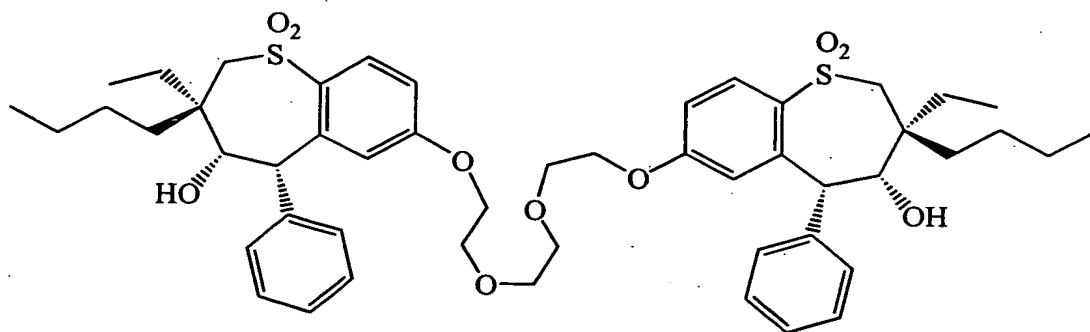
CPD # 101 (Example 59)



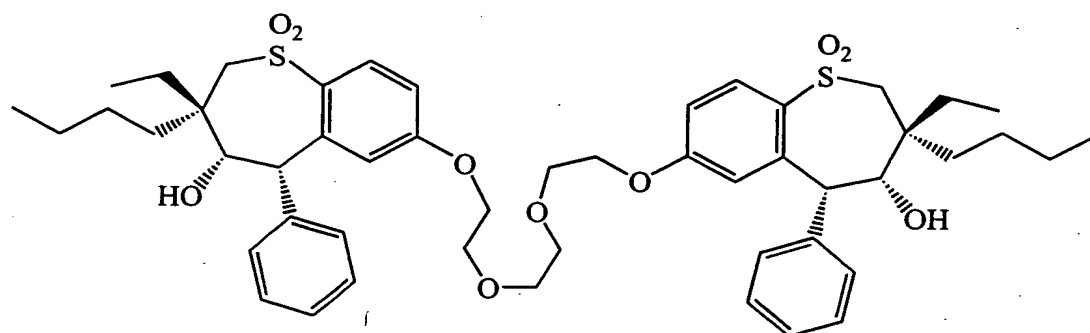
CPD #112 (Example 53)



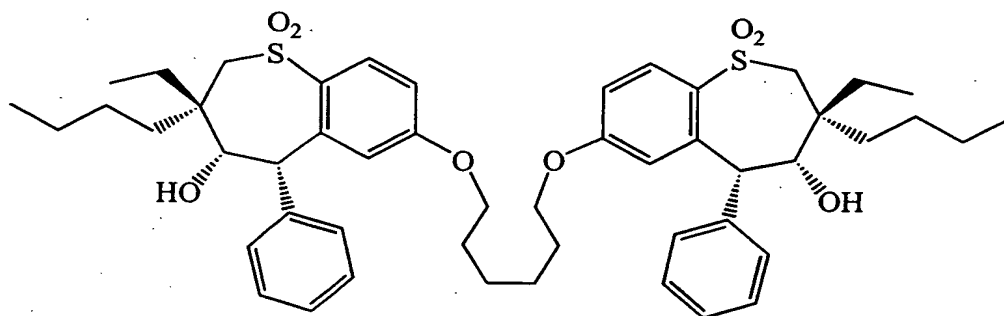
CPD #131 (Example 56)



CPD #135 (Example 55)

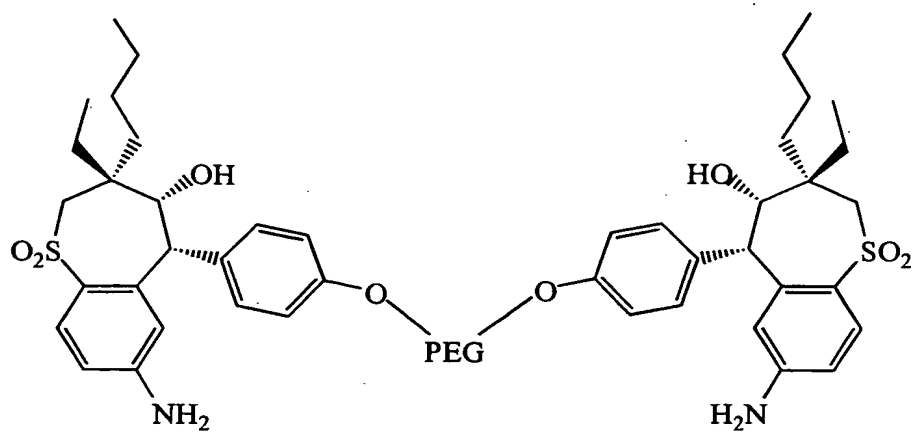


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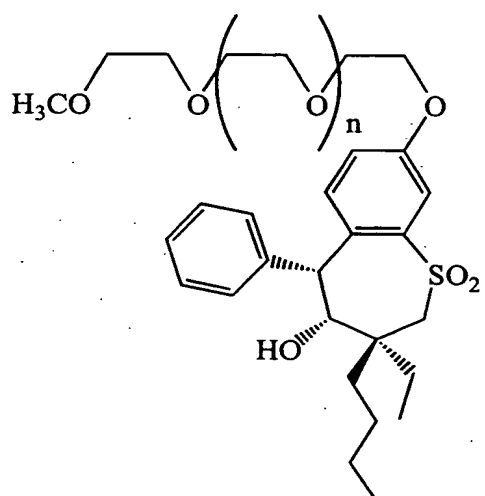
CPD #139 (Example 58)

[906]



PEG = 3400 molecular weight polyethyleneglycol bridge

CPD #140 (Example 51)

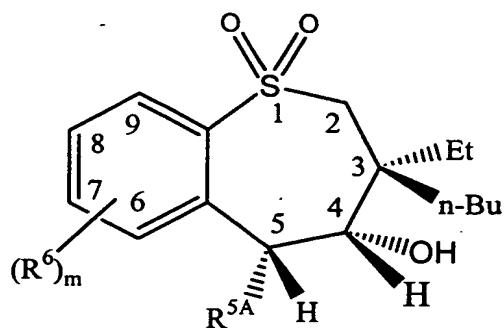


CPD #141 (Example 50)

[907] Examples 104-231

[908] Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, including where necessary other common synthesis expedients well known to the art, compounds are prepared having the structures set forth in Table 4 below. The starting materials illustrated in the reaction schemes shown above are varied in accordance with principles of organic synthesis well known to the art in order to introduce the indicated substituents in the 4- and 5- positions (R^{3A} , R^{3B} , R^{4A} , R^{5A}) and in the indicated position on the benzo ring (R^6). See Table 4 below.

Table 4: Alternative compounds #1 (#302-312, 314-430)



Cpd#	R ^{5A}	(R ⁶) _m
302	p-F-Ph-	7-(1-aziridine)
303	p-F-Ph-	7-EtS-
304	p-F-Ph-	7-CH ₃ S(O)-
305	p-F-Ph-	7-CH ₃ S(O) ₂ -
306	p-F-Ph-	7-PhS-
307	p-F-Ph-	7-CH ₃ S- 9-CH ₃ S-
308	p-F-Ph-	7-CH ₃ O- 9-CH ₃ O-
309	p-F-Ph-	7-Et-
310	p-F-Ph-	7-iPr-
311	p-F-Ph-	7-t-Bu-
312	p-F-Ph-	7-(1-pyrazole)-
314	m-CH ₃ O-Ph	7-(1-azetidine)
315	m-CH ₃ O-Ph-	7-(1-aziridine)
316	m-CH ₃ O-Ph-	7-EtS-
317	m-CH ₃ O-Ph-	7-CH ₃ S(O)-

Cpd#	R ^{5A}	(R ⁶) _m
318	m-CH ₃ O-Ph-	7-CH ₃ S(O) ₂ -
319	m-CH ₃ O-Ph-	7-PhS-
320	m-CH ₃ O-Ph	7-CH ₃ S- 9-CH ₃ S-
321	m-CH ₃ O-Ph	7-CH ₃ O- 9-CH ₃ O-
322	m-CH ₃ O-Ph	7-Et-
323	m-CH ₃ O-Ph	7-iPr-
324	m-CH ₃ O-Ph	7-t-Bu-
325	p-F-Ph-	6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O-
326	p-F-Ph-	7-(1-azetidine) 9-CH ₃ -
327	p-F-Ph-	7-EtS- 9-CH ₃ -
328	p-F-Ph-	7-CH ₃ S(O)- 9-CH ₃ -
329	p-F-Ph-	7-CH ₃ S(O) ₂ - 9-CH ₃ -
330	p-F-Ph-	7-PhS- 9-CH ₃ -
331	p-F-Ph-	7-CH ₃ S- 9-CH ₃ -
332	p-F-Ph-	7-CH ₃ O- 9-CH ₃ -
333	p-F-Ph-	7-CH ₃ - 9-CH ₃ -

Cpd#	R ^{5A}	(R ⁶) _m
334	p-F-Ph-	7-CH ₃ O- 9-CH ₃ O-
335	p-F-Ph-	7-(1-pyrrole)
336	p-F-Ph-	7-(N)N'-methylpiperazine
337	p-F-Ph-	Ph-
338	p-F-Ph-	7-CH ₃ C(=CH ₂)-
339	p-F-Ph-	7-cyclopropyl
340	p-F-Ph-	7-(CH ₃) ₂ NHN-
341	p-F-Ph-	7-(N)-azetidine 9-CH ₃ S-
342	p-F-Ph-	7-(N-pyrrolidine) 9-CH ₃ S-
343	p-F-Ph-	7-(CH ₃) ₂ N- 9-CH ₃ S-
344	m-CH ₃ O-Ph-	7-(1-pyrazole)
345	m-CH ₃ O-Ph-	7-(N)N'-methylpiperazine
346	m-CH ₃ O-Ph-	Ph-
347	m-CH ₃ O-Ph-	7-CH ₃ C(=CH ₂)-
348	m-CH ₃ O-Ph-	7-cyclopropyl
349	m-CH ₃ O-Ph-	7-(CH ₃) ₂ NHN-
350	m-CH ₃ O-Ph-	7-(N)-azetidine 9-CH ₃ S-
351	m-CH ₃ O-Ph-	7-(N-pyrrolidine)- 9-CH ₃ S-
352	m-CH ₃ O-Ph-	7-(CH ₃) ₂ N- 9-CH ₃ S-

Cpd#	R ^{5A}	(R ⁶) _m
353	m-CH ₃ O-Ph-	6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O-
354	m-CH ₃ O-Ph-	7-(1-azetidine) 9-CH ₃ -
355	m-CH ₃ O-Ph-	7-EtS- 9-CH ₃ -
356	m-CH ₃ O-Ph-	7-CH ₃ S(O)- 9-CH ₃ -
357	m-CH ₃ O-Ph-	7-CH ₃ S(O) ₂ - 9-CH ₃ -
358	m-CH ₃ O-Ph-	7-PhS- 9-CH ₃ -
359	m-CH ₃ O-Ph-	7-CH ₃ S- 9-CH ₃ -
360	m-CH ₃ O-Ph-	7-CH ₃ O- 9-CH ₃ -
361	m-CH ₃ O-Ph-	7-CH ₃ - 9-CH ₃ -
362	m-CH ₃ O-Ph-	7-CH ₃ O- 9-CH ₃ O-
363	thien-2-yl	7-(1-aziridine)
364	thien-2-yl	7-EtS-
365	thien-2-yl	7-CH ₃ S(O)-
366	thien-2-yl	7-CH ₃ S(O) ₂ -
367	thien-2-yl	7-PhS-
368	thien-2-yl	7-CH ₃ S- 9-CH ₃ S-

Cpd#	R ^{5A}	(R ⁶) _m
369	thien-2-yl	7-CH ₃ O- 9-CH ₃ O-
370	thien-2-yl	7-Et-
371	thien-2-yl	7-iPr-
372	thien-2-yl	7-t-Bu-
373	thien-2-yl	7-(1-pyrrole)-
374	thien-2-yl	7-CH ₃ O-
375	thien-2-yl	7-CH ₃ S-
376	thien-2-yl	7-(1-azetidine)
377	thien-2-yl	7-Me-
378	5-Cl-thien-2-yl	7-(1-azetidine)
379	5-Cl-thien-2-yl	7-(1-aziridine)
380	5-Cl-thien-2-yl	7-EtS-
381	5-Cl-thien-2-yl	7-CH ₃ S(O)-
382	5-Cl-thien-2-yl	7-CH ₃ S(O) ₂ -
383	5-Cl-thien-2-yl	7-PhS-
384	5-Cl-thien-2-yl	7-CH ₃ S- 9-CH ₃ S-
385	5-Cl-thien-2-yl	7-CH ₃ O- 9-CH ₃ O-
386	5-Cl-thien-2-yl	7-Et-
387	5-Cl-thien-2-yl	7-iPr-
388	5-Cl-thien-2-yl	7-t-Bu-
389	5-Cl-thien-2-yl	7-CH ₃ O-
390	5-Cl-thien-2-yl	7-CH ₃ S-

Cpd#	R ^{5A}	(R ⁶) _m
391	5-Cl-thien-2-yl	7-Me
392	thien-2-yl	7-(1-azetidine) 9-CH ₃ -
393	thien-2-yl	7-EtS- 9-CH ₃ -
394	thien-2-yl	7-CH ₃ S(O)- 9-CH ₃ -
395	thien-2-yl	7-CH ₃ S(O) ₂ - 9-CH ₃ -
396	thien-2-yl	7-PhS- 9-CH ₃ -
397	thien-2-yl	7-CH ₃ S- 9-CH ₃ -
398	thien-2-yl	7-CH ₃ O- 9-CH ₃ -
399	thien-2-yl	7-CH ₃ - 9-CH ₃ -
400	thien-2-yl	7-CH ₃ O- 9-CH ₃ O-
401	thien-2-yl	7-(1-pyrazole)
402	thien-2-yl	7-(N)N'-methylpiperazine
403	thien-2-yl	Ph-
404	thien-2-yl	7-CH ₃ C(=CH ₂)-
405	thien-2-yl	7-cyclpropyl
406	thien-2-yl	7-(CH ₃) ₂ NHN-
407	thien-2-yl	7-(N)-azetidine 9-CH ₃ S-

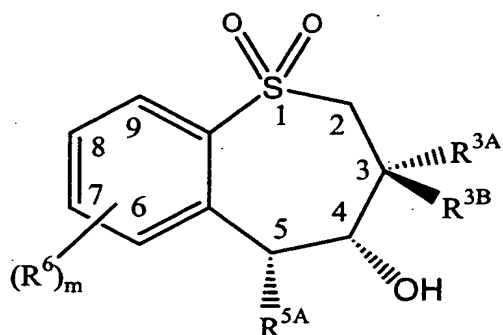
Cpd#	R ^{5A}	(R ⁶) _m
408	thien-2-yl	7-(N-pyrrolidine) 9-CH ₃ S-
409	thien-2-yl	7-(CH ₃) ₂ N- 9-CH ₃ S-
411	5-Cl-thien-2-yl	7-(1-pyrazole)
412	5-Cl-thien-2-yl	7-(N)N'-methylpiperazine
413	5-Cl-thien-2-yl	Ph-
414	5-Cl-thien-2-yl	7-CH ₃ C(=CH ₂)-
415	5-Cl-thien-2-yl	7-cyclopropyl
416	5-Cl-thien-2-yl	7-(CH ₃) ₂ NHN-
417	5-Cl-thien-2-yl	7-(N)-azetidine 9-CH ₃ S-
418	5-Cl-thien-2-yl	7-(N-pyrrolidine)- 9-CH ₃ S-
419	5-Cl-thien-2-yl	7-(CH ₃) ₂ N- 9-CH ₃ S-
420	5-Cl-thien-2-yl	7-(1-azetidine) 9-CH ₃ -
421	5-Cl-thien-2-yl	7-EtS- 9-CH ₃ -
422	5-Cl-thien-2-yl	7-CH ₃ S(O)- 9-CH ₃ -
423	5-Cl-thien-2-yl	7-CH ₃ S(O) ₂ - 9-CH ₃ -
424	5-Cl-thien-2-yl	7-PhS- 9-CH ₃ -
425	5-Cl-thien-2-yl	7-CH ₃ S- 9-CH ₃ -

Cpd#	R ^{5A}	(R ⁶) _m
426	5-Cl-thien-2-yl	7-CH ₃ O- 9-CH ₃ -
427	5-Cl-thien-2-yl	7-CH ₃ - 9-CH ₃ -
428	5-Cl-thien-2-yl	7-CH ₃ O- 9-CH ₃ O-
429	thien-2-yl	6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O-
430	5-Cl-thien-2-yl	6-CH ₃ O- 7-CH ₃ O- 8-CH ₃ O-

[909] Examples 232-1394

[910] Using in each instance a method generally described in those of Examples 1 to 72 appropriate to the substituents to be introduced, including where necessary other common synthesis expedients well known to the art, compounds are prepared having the structures set forth in Table 5-7 below. The starting materials illustrated in the reaction schemes shown above are varied in accordance with principles of organic synthesis well known to the art in order to introduce the indicated substituents in the 4- and 5- positions (R^{3A}, R^{3B}, R^{4A}, R^{5A}) and in the indicated position on the benzo ring (R⁶).

Table 5



Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
F101.001	01	Ethyl	Ph-	7-methyl
	02	Ethyl	Ph-	7-ethyl
	03	Ethyl	Ph-	7-iso-propyl
	04	Ethyl	Ph-	7-tert-butyl
	05	Ethyl	Ph-	7-OH
	06	Ethyl	Ph-	7-OCH ₃
	07	Ethyl	Ph-	7-O(iso-propyl)
	08	Ethyl	Ph-	7-SCH ₃
	09	Ethyl	Ph-	7-SOCH ₃
	10	ethyl	Ph-	7-SO ₂ CH ₃
	11	ethyl	Ph-	7-SCH ₂ CH ₃
	12	ethyl	Ph-	7-NH ₂
	13	ethyl	Ph-	7-NHOH
	14	ethyl	Ph-	7-NHCH ₃
	15	ethyl	Ph-	7-N(CH ₃) ₂
	16	ethyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	ethyl	Ph-	7-NHC(=O)CH ₃
	18	ethyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	ethyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	ethyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	ethyl	Ph-	7-(N)-morpholine
	22	ethyl	Ph-	7-(N)-azetidine
	23	ethyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	ethyl	Ph-	7-(N)-pyrrolidine

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	25	ethyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	ethyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	ethyl	Ph-	7-(N)-N'-methylpiperazine
	28	ethyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	ethyl	Ph-	7-NH-CBZ
	30	ethyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	ethyl	Ph-	7-NHC(O)CH ₂ Br
	32	ethyl	Ph-	7-NH-C(NH)NH ₂
	33	ethyl	Ph-	7-(2)-thiophene
	34	ethyl	Ph-	8-methyl
	35	ethyl	Ph-	8-ethyl
	36	ethyl	Ph-	8-iso-propyl
	37	ethyl	Ph-	8-tert-butyl
	38	ethyl	Ph-	8-OH
	39	ethyl	Ph-	8-OCH ₃
	40	ethyl	Ph-	8-O(iso-propyl)
	41	ethyl	Ph-	8-SCH ₃
	42	ethyl	Ph-	8-SOCH ₃
	43	ethyl	Ph-	8-SO ₂ CH ₃
	44	ethyl	Ph-	8-SCH ₂ CH ₃
	45	ethyl	Ph-	8-NH ₂
	46	ethyl	Ph-	8-NHOH
	47	ethyl	Ph-	8-NHCH ₃
	48	ethyl	Ph-	8-N(CH ₃) ₂
	49	ethyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	ethyl	Ph-	8-NHC(=O)CH ₃
	51	ethyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	ethyl	Ph-	8-NMeCH ₂ CO ₂ H
	53	ethyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	ethyl	Ph-	8-(N)-morpholine
	55	ethyl	Ph-	8-(N)-azetidine
	56	ethyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	ethyl	Ph-	8-(N)-pyrrolidine
	58	ethyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	ethyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	ethyl	Ph-	8-(N)-N'-methylpiperazine
	61	ethyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	ethyl	Ph-	8-NH-CBZ

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	63	ethyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	ethyl	Ph-	8-NHC(O)CH ₂ Br
	65	ethyl	Ph-	8-NH-C(NH)NH ₂
	66	ethyl	Ph-	8-(2)-thiophene
	67	ethyl	Ph-	9-methyl
	68	ethyl	Ph-	9-ethyl
	69	ethyl	Ph-	9-iso-propyl
	70	ethyl	Ph-	9-tert-butyl
	71	ethyl	Ph-	9-OH
	72	ethyl	Ph-	9-OCH ₃
	73	ethyl	Ph-	9-O(iso-propyl)
	74	ethyl	Ph-	9-SCH ₃
	75	ethyl	Ph-	9-SOCH ₃
	76	ethyl	Ph-	9-SO ₂ CH ₃
	77	ethyl	Ph-	9-SCH ₂ CH ₃
	78	ethyl	Ph-	9-NH ₂
	79	ethyl	Ph-	9-NHOH
	80	ethyl	Ph-	9-NHCH ₃
	81	ethyl	Ph-	9-N(CH ₃) ₂
	82	ethyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	ethyl	Ph-	9-NHC(=O)CH ₃
	84	ethyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	ethyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	ethyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	ethyl	Ph-	9-(N)-morpholine
	88	ethyl	Ph-	9-(N)-azetidine
	89	ethyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	ethyl	Ph-	9-(N)-pyrrolidine
	91	ethyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	ethyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	ethyl	Ph-	9-(N)-N'-methylpiperazine
	93	ethyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	ethyl	Ph-	9-NH-CBZ
	96	ethyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	ethyl	Ph-	9-NHC(O)CH ₂ Br
	98	ethyl	Ph-	9-NH-C(NH)NH ₂
	99	ethyl	Ph-	9-(2)-thiophene

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	100	ethyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	ethyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	ethyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	ethyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.002	01	n-propyl	Ph-	7-methyl
	02	n-propyl	Ph-	7-ethyl
	03	n-propyl	Ph-	7-iso-propyl
	04	n-propyl	Ph-	7-tert-butyl
	05	n-propyl	Ph-	7-OH
	06	n-propyl	Ph-	7-OCH ₃
	07	n-propyl	Ph-	7-O(iso-propyl)
	08	n-propyl	Ph-	7-SCH ₃
	09	n-propyl	Ph-	7-SOCH ₃
	10	n-propyl	Ph-	7-SO ₂ CH ₃
	11	n-propyl	Ph-	7-SCH ₂ CH ₃
	12	n-propyl	Ph-	7-NH ₂
	13	n-propyl	Ph-	7-NHOH
	14	n-propyl	Ph-	7-NHCH ₃
	15	n-propyl	Ph-	7-N(CH ₃) ₂
	16	n-propyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	n-propyl	Ph-	7-NHC(=O)CH ₃
	18	n-propyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	n-propyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	n-propyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	n-propyl	Ph-	7-(N)-morpholine
	22	n-propyl	Ph-	7-(N)-azetidine
	23	n-propyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	n-propyl	Ph-	7-(N)-pyrrolidine
	25	n-propyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	n-propyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	n-propyl	Ph-	7-(N)-N'-methylpiperazine
	28	n-propyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	n-propyl	Ph-	7-NH-CBZ
	30	n-propyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	n-propyl	Ph-	7-NHC(O)CH ₂ Br
	32	n-propyl	Ph-	7-NH-C(NH)NH ₂
	33	n-propyl	Ph-	7-(2)-thiophene
	34	n-propyl	Ph-	8-methyl

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	35	n-propyl	Ph-	8-ethyl
	36	n-propyl	Ph-	8-iso-propyl
	37	n-propyl	Ph-	8-tert-butyl
	38	n-propyl	Ph-	8-OH
	39	n-propyl	Ph-	8-OCH ₃
	40	n-propyl	Ph-	8-O(iso-propyl)
	41	n-propyl	Ph-	8-SCH ₃
	42	n-propyl	Ph-	8-SOCH ₃
	43	n-propyl	Ph-	8-SO ₂ CH ₃
	44	n-propyl	Ph-	8-SCH ₂ CH ₃
	45	n-propyl	Ph-	8-NH ₂
	46	n-propyl	Ph-	8-NHOH
	47	n-propyl	Ph-	8-NHCH ₃
	48	n-propyl	Ph-	8-N(CH ₃) ₂
	49	n-propyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	n-propyl	Ph-	8-NHC(=O)CH ₃
	51	n-propyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	n-propyl	Ph-	8-NMeCH ₂ CO ₂ H
	53	n-propyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	n-propyl	Ph-	8-(N)-morpholine
	55	n-propyl	Ph-	8-(N)-azetidine
	56	n-propyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	n-propyl	Ph-	8-(N)-pyrrolidine
	58	n-propyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	n-propyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	n-propyl	Ph-	8-(N)-N'-methylpiperazine
	61	n-propyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	n-propyl	Ph-	8-NH-CBZ
	63	n-propyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	n-propyl	Ph-	8-NHC(O)CH ₂ Br
	65	n-propyl	Ph-	8-NH-C(NH)NH ₂
	66	n-propyl	Ph-	8-(2)-thiophene
	67	n-propyl	Ph-	9-methyl
	68	n-propyl	Ph-	9-ethyl
	69	n-propyl	Ph-	9-iso-propyl
	70	n-propyl	Ph-	9-tert-butyl
	71	n-propyl	Ph-	9-OH
	72	n-propyl	Ph-	9-OCH ₃

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	73	n-propyl	Ph-	9-O(iso-propyl)
	74	n-propyl	Ph-	9-SCH ₃
	75	n-propyl	Ph-	9-SOCH ₃
	76	n-propyl	Ph-	9-SO ₂ CH ₃
	77	n-propyl	Ph-	9-SCH ₂ CH ₃
	78	n-propyl	Ph-	9-NH ₂
	79	n-propyl	Ph-	9-NHOH
	80	n-propyl	Ph-	9-NHCH ₃
	81	n-propyl	Ph-	9-N(CH ₃) ₂
	82	n-propyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	n-propyl	Ph-	9-NHC(=O)CH ₃
	84	n-propyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	n-propyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	n-propyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	n-propyl	Ph-	9-(N)-morpholine
	88	n-propyl	Ph-	9-(N)-azetidine
	89	n-propyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	n-propyl	Ph-	9-(N)-pyrrolidine
	91	n-propyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	n-propyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	n-propyl	Ph-	9-(N)-N'-methylpiperazine
	93	n-propyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	n-propyl	Ph-	9-NH-CBZ
	96	n-propyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	n-propyl	Ph-	9-NHC(O)CH ₂ Br
	98	n-propyl	Ph-	9-NH-C(NH)NH ₂
	99	n-propyl	Ph-	9-(2)-thiophene
	100	n-propyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	n-propyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	n-propyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	n-propyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.003	01	n-butyl	Ph-	7-methyl
	02	n-butyl	Ph-	7-ethyl
	03	n-butyl	Ph-	7-iso-propyl
	04	n-butyl	Ph-	7-tert-butyl
	05	n-butyl	Ph-	7-OH
	06	n-butyl	Ph-	7-OCH ₃
	07	n-butyl	Ph-	7-O(iso-propyl)

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	08	n-butyl	Ph-	7-SCH ₃
	09	n-butyl	Ph-	7-SOCH ₃
	10	n-butyl	Ph-	7-SO ₂ CH ₃
	11	n-butyl	Ph-	7-SCH ₂ CH ₃
	12	n-butyl	Ph-	7-NH ₂
	13	n-butyl	Ph-	7-NHOH
	14	n-butyl	Ph-	7-NHCH ₃
	15	n-butyl	Ph-	7-N(CH ₃) ₂
	16	n-butyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	n-butyl	Ph-	7-NHC(=O)CH ₃
	18	n-butyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	n-butyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	n-butyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	n-butyl	Ph-	7-(N)-morpholine
	22	n-butyl	Ph-	7-(N)-azetidine
	23	n-butyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	n-butyl	Ph-	7-(N)-pyrrolidine
	25	n-butyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	n-butyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	n-butyl	Ph-	7-(N)-N'-methylpiperazine
	28	n-butyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	n-butyl	Ph-	7-NH-CBZ
	30	n-butyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	n-butyl	Ph-	7-NHC(O)CH ₂ Br
	32	n-butyl	Ph-	7-NH-C(NH)NH ₂
	33	n-butyl	Ph-	7-(2)-thiophene
	34	n-butyl	Ph-	8-methyl
	35	n-butyl	Ph-	8-ethyl
	36	n-butyl	Ph-	8-iso-propyl
	37	n-butyl	Ph-	8-tert-butyl
	38	n-butyl	Ph-	8-OH
	39	n-butyl	Ph-	8-OCH ₃
	40	n-butyl	Ph-	8-O(iso-propyl)
	41	n-butyl	Ph-	8-SCH ₃
	42	n-butyl	Ph-	8-SOCH ₃
	43	n-butyl	Ph-	8-SO ₂ CH ₃
	44	n-butyl	Ph-	8-SCH ₂ CH ₃

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	45	n-butyl	Ph-	8-NH ₂
	46	n-butyl	Ph-	8-NHOH
	47	n-butyl	Ph-	8-NHCH ₃
	48	n-butyl	Ph-	8-N(CH ₃) ₂
	49	n-butyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	n-butyl	Ph-	8-NHC(=O)CH ₃
	51	n-butyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	n-butyl	Ph-	8-NMeCH ₂ CO ₂ H
	53	n-butyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	n-butyl	Ph-	8-(N)-morpholine
	55	n-butyl	Ph-	8-(N)-azetidine
	56	n-butyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	n-butyl	Ph-	8-(N)-pyrrolidine
	58	n-butyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	n-butyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	n-butyl	Ph-	8-(N)-N'-methylpiperazine
	61	n-butyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	n-butyl	Ph-	8-NH-CBZ
	63	n-butyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	n-butyl	Ph-	8-NHC(O)CH ₂ Br
	65	n-butyl	Ph-	8-NH-C(NH)NH ₂
	66	n-butyl	Ph-	8-(2)-thiophene
	67	n-butyl	Ph-	9-methyl
	68	n-butyl	Ph-	9-ethyl
	69	n-butyl	Ph-	9-iso-propyl
	70	n-butyl	Ph-	9-tert-butyl
	71	n-butyl	Ph-	9-OH
	72	n-butyl	Ph-	9-OCH ₃
	73	n-butyl	Ph-	9-O(iso-propyl)
	74	n-butyl	Ph-	9-SCH ₃
	75	n-butyl	Ph-	9-SOCH ₃
	76	n-butyl	Ph-	9-SO ₂ CH ₃
	77	n-butyl	Ph-	9-SCH ₂ CH ₃
	78	n-butyl	Ph-	9-NH ₂
	79	n-butyl	Ph-	9-NHOH
	80	n-butyl	Ph-	9-NHCH ₃
	81	n-butyl	Ph-	9-N(CH ₃) ₂

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	82	n-butyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	n-butyl	Ph-	9-NHC(=O)CH ₃
	84	n-butyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	n-butyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	n-butyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	n-butyl	Ph-	9-(N)-morpholine
	88	n-butyl	Ph-	9-(N)-azetidine
	89	n-butyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	n-butyl	Ph-	9-(N)-pyrrolidine
	91	n-butyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	n-butyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	n-butyl	Ph-	9-(N)-N'-methylpiperazine
	93	n-butyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	n-butyl	Ph-	9-NH-CBZ
	96	n-butyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	n-butyl	Ph-	9-NHC(O)CH ₂ Br
	98	n-butyl	Ph-	9-NH-C(NH)NH ₂
	99	n-butyl	Ph-	9-(2)-thiophene
	100	n-butyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	n-butyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	n-butyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	n-butyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.004	01	n-pentyl	Ph-	7-methyl
	02	n-pentyl	Ph-	7-ethyl
	03	n-pentyl	Ph-	7-iso-propyl
	04	n-pentyl	Ph-	7-tert-butyl
	05	n-pentyl	Ph-	7-OH
	06	n-pentyl	Ph-	7-OCH ₃
	07	n-pentyl	Ph-	7-O(iso-propyl)
	08	n-pentyl	Ph-	7-SCH ₃
	09	n-pentyl	Ph-	7-SOCH ₃
	10	n-pentyl	Ph-	7-SO ₂ CH ₃
	11	n-pentyl	Ph-	7-SCH ₂ CH ₃
	12	n-pentyl	Ph-	7-NH ₂
	13	n-pentyl	Ph-	7-NHOH
	14	n-pentyl	Ph-	7-NHCH ₃
	15	n-pentyl	Ph-	7-N(CH ₃) ₂

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R5A	(R ⁶) _m
	16	n-pentyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	n-pentyl	Ph-	7-NHC(=O)CH ₃
	18	n-pentyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	n-pentyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	n-pentyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	n-pentyl	Ph-	7-(N)-morpholine
	22	n-pentyl	Ph-	7-(N)-azetidine
	23	n-pentyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	n-pentyl	Ph-	7-(N)-pyrrolidine
	25	n-pentyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	n-pentyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	n-pentyl	Ph-	7-(N)-N'-methylpiperazine
	28	n-pentyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	n-pentyl	Ph-	7-NH-CBZ
	30	n-pentyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	n-pentyl	Ph-	7-NHC(O)CH ₂ Br
	32	n-pentyl	Ph-	7-NH-C(NH)NH ₂
	33	n-pentyl	Ph-	7-(2)-thiophene
	34	n-pentyl	Ph-	8-methyl
	35	n-pentyl	Ph-	8-ethyl
	36	n-pentyl	Ph-	8-iso-propyl
	37	n-pentyl	Ph-	8-tert-butyl
	38	n-pentyl	Ph-	8-OH
	39	n-pentyl	Ph-	8-OCH ₃
	40	n-pentyl	Ph-	8-O(iso-propyl)
	41	n-pentyl	Ph-	8-SCH ₃
	42	n-pentyl	Ph-	8-SOCH ₃
	43	n-pentyl	Ph-	8-SO ₂ CH ₃
	44	n-pentyl	Ph-	8-SCH ₂ CH ₃
	45	n-pentyl	Ph-	8-NH ₂
	46	n-pentyl	Ph-	8-NHOH
	47	n-pentyl	Ph-	8-NHCH ₃
	48	n-pentyl	Ph-	8-N(CH ₃) ₂
	49	n-pentyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	n-pentyl	Ph-	8-NHC(=O)CH ₃
	51	n-pentyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	n-pentyl	Ph-	8-NMeCH ₂ CO ₂ H

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	53	n-pentyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	n-pentyl	Ph-	8-(N)-morpholine
	55	n-pentyl	Ph-	8-(N)-azetidine
	56	n-pentyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	n-pentyl	Ph-	8-(N)-pyrrolidine
	58	n-pentyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	n-pentyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	n-pentyl	Ph-	8-(N)-N'-methylpiperazine
	61	n-pentyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	n-pentyl	Ph-	8-NH-CBZ
	63	n-pentyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	n-pentyl	Ph-	8-NHC(O)CH ₂ Br
	65	n-pentyl	Ph-	8-NH-C(NH)NH ₂
	66	n-pentyl	Ph-	8-(2)-thiophene
	67	n-pentyl	Ph-	9-methyl
	68	n-pentyl	Ph-	9-ethyl
	69	n-pentyl	Ph-	9-iso-propyl
	70	n-pentyl	Ph-	9-tert-butyl
	71	n-pentyl	Ph-	9-OH
	72	n-pentyl	Ph-	9-OCH ₃
	73	n-pentyl	Ph-	9-O(iso-propyl)
	74	n-pentyl	Ph-	9-SCH ₃
	75	n-pentyl	Ph-	9-SOCH ₃
	76	n-pentyl	Ph-	9-SO ₂ CH ₃
	77	n-pentyl	Ph-	9-SCH ₂ CH ₃
	78	n-pentyl	Ph-	9-NH ₂
	79	n-pentyl	Ph-	9-NHOH
	80	n-pentyl	Ph-	9-NHCH ₃
	81	n-pentyl	Ph-	9-N(CH ₃) ₂
	82	n-pentyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	n-pentyl	Ph-	9-NHC(=O)CH ₃
	84	n-pentyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	n-pentyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	n-pentyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	n-pentyl	Ph-	9-(N)-morpholine
	88	n-pentyl	Ph-	9-(N)-azetidine
	89	n-pentyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	n-pentyl	Ph-	9-(N)-pyrrolidine

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	91	n-pentyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	n-pentyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	n-pentyl	Ph-	9-(N)-N'-methylpiperazine
	93	n-pentyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	n-pentyl	Ph-	9-NH-CBZ
	96	n-pentyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	n-pentyl	Ph-	9-NHC(O)CH ₂ Br
	98	n-pentyl	Ph-	9-NH-C(NH)NH ₂
	99	n-pentyl	Ph-	9-(2)-thiophene
	100	n-pentyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	n-pentyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	n-pentyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	n-pentyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.005	01	n-hexyl	Ph-	7-methyl
	02	n-hexyl	Ph-	7-ethyl
	03	n-hexyl	Ph-	7-iso-propyl
	04	n-hexyl	Ph-	7-tert-butyl
	05	n-hexyl	Ph-	7-OH
	06	n-hexyl	Ph-	7-OCH ₃
	07	n-hexyl	Ph-	7-O(iso-propyl)
	08	n-hexyl	Ph-	7-SCH ₃
	09	n-hexyl	Ph-	7-SOCH ₃
	10	n-hexyl	Ph-	7-SO ₂ CH ₃
	11	n-hexyl	Ph-	7-SCH ₂ CH ₃
	12	n-hexyl	Ph-	7-NH ₂
	13	n-hexyl	Ph-	7-NHOH
	14	n-hexyl	Ph-	7-NHCH ₃
	15	n-hexyl	Ph-	7-N(CH ₃) ₂
	16	n-hexyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	n-hexyl	Ph-	7-NHC(=O)CH ₃
	18	n-hexyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	n-hexyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	n-hexyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	n-hexyl	Ph-	7-(N)-morpholine
	22	n-hexyl	Ph-	7-(N)-azetidine
	23	n-hexyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	n-hexyl	Ph-	7-(N)-pyrrolidine

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	25	n-hexyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	n-hexyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	n-hexyl	Ph-	7-(N)-N'-methylpiperazine
	28	n-hexyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	n-hexyl	Ph-	7-NH-CBZ
	30	n-hexyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	n-hexyl	Ph-	7-NHC(O)CH ₂ Br
	32	n-hexyl	Ph-	7-NH-C(NH)NH ₂
	33	n-hexyl	Ph-	7-(2)-thiophene
	34	n-hexyl	Ph-	8-methyl
	35	n-hexyl	Ph-	8-ethyl
	36	n-hexyl	Ph-	8-iso-propyl
	37	n-hexyl	Ph-	8-tert-butyl
	38	n-hexyl	Ph-	8-OH
	39	n-hexyl	Ph-	8-OCH ₃
	40	n-hexyl	Ph-	8-O(iso-propyl)
	41	n-hexyl	Ph-	8-SCH ₃
	42	n-hexyl	Ph-	8-SOCH ₃
	43	n-hexyl	Ph-	8-SO ₂ CH ₃
	44	n-hexyl	Ph-	8-SCH ₂ CH ₃
	45	n-hexyl	Ph-	8-NH ₂
	46	n-hexyl	Ph-	8-NHOH
	47	n-hexyl	Ph-	8-NHCH ₃
	48	n-hexyl	Ph-	8-N(CH ₃) ₂
	49	n-hexyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	n-hexyl	Ph-	8-NHC(=O)CH ₃
	51	n-hexyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	n-hexyl	Ph-	8-NMeCH ₂ CO ₂ H
	53	n-hexyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	n-hexyl	Ph-	8-(N)-morpholine
	55	n-hexyl	Ph-	8-(N)-azetidine
	56	n-hexyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	n-hexyl	Ph-	8-(N)-pyrrolidine
	58	n-hexyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	n-hexyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	n-hexyl	Ph-	8-(N)-N'-methylpiperazine
	61	n-hexyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	n-hexyl	Ph-	8-NH-CBZ

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	63	n-hexyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	n-hexyl	Ph-	8-NHC(O)CH ₂ Br
	65	n-hexyl	Ph-	8-NH-C(NH)NH ₂
	66	n-hexyl	Ph-	8-(2)-thiophene
	67	n-hexyl	Ph-	9-methyl
	68	n-hexyl	Ph-	9-ethyl
	69	n-hexyl	Ph-	9-iso-propyl
	70	n-hexyl	Ph-	9-tert-butyl
	71	n-hexyl	Ph-	9-OH
	72	n-hexyl	Ph-	9-OCH ₃
	73	n-hexyl	Ph-	9-O(iso-propyl)
	74	n-hexyl	Ph-	9-SCH ₃
	75	n-hexyl	Ph-	9-SOCH ₃
	76	n-hexyl	Ph-	9-SO ₂ CH ₃
	77	n-hexyl	Ph-	9-SCH ₂ CH ₃
	78	n-hexyl	Ph-	9-NH ₂
	79	n-hexyl	Ph-	9-NHOH
	80	n-hexyl	Ph-	9-NHCH ₃
	81	n-hexyl	Ph-	9-N(CH ₃) ₂
	82	n-hexyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	n-hexyl	Ph-	9-NHC(=O)CH ₃
	84	n-hexyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	n-hexyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	n-hexyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	n-hexyl	Ph-	9-(N)-morpholine
	88	n-hexyl	Ph-	9-(N)-azetidine
	89	n-hexyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	n-hexyl	Ph-	9-(N)-pyrrolidine
	91	n-hexyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	n-hexyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	n-hexyl	Ph-	9-(N)-N'-methylpiperazine
	93	n-hexyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	n-hexyl	Ph-	9-NH-CBZ
	96	n-hexyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	n-hexyl	Ph-	9-NHC(O)CH ₂ Br
	98	n-hexyl	Ph-	9-NH-C(NH)NH ₂
	99	n-hexyl	Ph-	9-(2)-thiophene

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	100	n-hexyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	n-hexyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	n-hexyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	n-hexyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.006	01	iso-propyl	Ph-	7-methyl
	02	iso-propyl	Ph-	7-ethyl
	03	iso-propyl	Ph-	7-iso-propyl
	04	iso-propyl	Ph-	7-tert-butyl
	05	iso-propyl	Ph-	7-OH
	06	iso-propyl	Ph-	7-OCH ₃
	07	iso-propyl	Ph-	7-O(iso-propyl)
	08	iso-propyl	Ph-	7-SCH ₃
	09	iso-propyl	Ph-	7-SOCH ₃
	10	iso-propyl	Ph-	7-SO ₂ CH ₃
	11	iso-propyl	Ph-	7-SCH ₂ CH ₃
	12	iso-propyl	Ph-	7-NH ₂
	13	iso-propyl	Ph-	7-NHOH
	14	iso-propyl	Ph-	7-NHCH ₃
	15	iso-propyl	Ph-	7-N(CH ₃) ₂
	16	iso-propyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	iso-propyl	Ph-	7-NHC(=O)CH ₃
	18	iso-propyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	iso-propyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	iso-propyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	iso-propyl	Ph-	7-(N)-morpholine
	22	iso-propyl	Ph-	7-(N)-azetidine
	23	iso-propyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	iso-propyl	Ph-	7-(N)-pyrrolidine
	25	iso-propyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	iso-propyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	iso-propyl	Ph-	7-(N)-N'-methylpiperazine
	28	iso-propyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	iso-propyl	Ph-	7-NH-CBZ
	30	iso-propyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	iso-propyl	Ph-	7-NHC(O)CH ₂ Br
	32	iso-propyl	Ph-	7-NH-C(NH)NH ₂
	33	iso-propyl	Ph-	7-(2)-thiophene
	34	iso-propyl	Ph-	8-methyl

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	35	iso-propyl	Ph-	8-ethyl
	36	iso-propyl	Ph-	8-iso-propyl
	37	iso-propyl	Ph-	8-tert-butyl
	38	iso-propyl	Ph-	8-OH
	39	iso-propyl	Ph-	8-OCH ₃
	40	iso-propyl	Ph-	8-O(iso-propyl)
	41	iso-propyl	Ph-	8-SCH ₃
	42	iso-propyl	Ph-	8-SOCH ₃
	43	iso-propyl	Ph-	8-SO ₂ CH ₃
	44	iso-propyl	Ph-	8-SCH ₂ CH ₃
	45	iso-propyl	Ph-	8-NH ₂
	46	iso-propyl	Ph-	8-NHOH
	47	iso-propyl	Ph-	8-NHCH ₃
	48	iso-propyl	Ph-	8-N(CH ₃) ₂
	49	iso-propyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	iso-propyl	Ph-	8-NHC(=O)CH ₃
	51	iso-propyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	iso-propyl	Ph-	8-NMeCH ₂ CO ₂ H
	53	iso-propyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	iso-propyl	Ph-	8-(N)-morpholine
	55	iso-propyl	Ph-	8-(N)-azetidine
	56	iso-propyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	iso-propyl	Ph-	8-(N)-pyrrolidine
	58	iso-propyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	iso-propyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	iso-propyl	Ph-	8-(N)-N'-methylpiperazine
	61	iso-propyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	iso-propyl	Ph-	8-NH-CBZ
	63	iso-propyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	iso-propyl	Ph-	8-NHC(O)CH ₂ Br
	65	iso-propyl	Ph-	8-NH-C(NH)NH ₂
	66	iso-propyl	Ph-	8-(2)-thiophene
	67	iso-propyl	Ph-	9-methyl
	68	iso-propyl	Ph-	9-ethyl
	69	iso-propyl	Ph-	9-iso-propyl
	70	iso-propyl	Ph-	9-tert-butyl
	71	iso-propyl	Ph-	9-OH
	72	iso-propyl	Ph-	9-OCH ₃

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	73	iso-propyl	Ph-	9-O(iso-propyl)
	74	iso-propyl	Ph-	9-SCH ₃
	75	iso-propyl	Ph-	9-SOCH ₃
	76	iso-propyl	Ph-	9-SO ₂ CH ₃
	77	iso-propyl	Ph-	9-SCH ₂ CH ₃
	78	iso-propyl	Ph-	9-NH ₂
	79	iso-propyl	Ph-	9-NHOH
	80	iso-propyl	Ph-	9-NHCH ₃
	81	iso-propyl	Ph-	9-N(CH ₃) ₂
	82	iso-propyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	iso-propyl	Ph-	9-NHC(=O)CH ₃
	84	iso-propyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	iso-propyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	iso-propyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	iso-propyl	Ph-	9-(N)-morpholine
	88	iso-propyl	Ph-	9-(N)-azetidine
	89	iso-propyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	iso-propyl	Ph-	9-(N)-pyrrolidine
	91	iso-propyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	iso-propyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	iso-propyl	Ph-	9-(N)-N'-methylpiperazine
	93	iso-propyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	iso-propyl	Ph-	9-NH-CBZ
	96	iso-propyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	iso-propyl	Ph-	9-NHC(O)CH ₂ Br
	98	iso-propyl	Ph-	9-NH-C(NH)NH ₂
	99	iso-propyl	Ph-	9-(2)-thiophene
	100	iso-propyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	iso-propyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	iso-propyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	iso-propyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.007	01	iso-butyl	Ph-	7-methyl
	02	iso-butyl	Ph-	7-ethyl
	03	iso-butyl	Ph-	7-iso-propyl
	04	iso-butyl	Ph-	7-tert-butyl
	05	iso-butyl	Ph-	7-OH
	06	iso-butyl	Ph-	7-OCH ₃
	07	iso-butyl	Ph-	7-O(iso-propyl)

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	08	iso-butyl	Ph-	7-SCH ₃
	09	iso-butyl	Ph-	7-SOCH ₃
	10	iso-butyl	Ph-	7-SO ₂ CH ₃
	11	iso-butyl	Ph-	7-SCH ₂ CH ₃
	12	iso-butyl	Ph-	7-NH ₂
	13	iso-butyl	Ph-	7-NHOH
	14	iso-butyl	Ph-	7-NHCH ₃
	15	iso-butyl	Ph-	7-N(CH ₃) ₂
	16	iso-butyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	iso-butyl	Ph-	7-NHC(=O)CH ₃
	18	iso-butyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	iso-butyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	iso-butyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	iso-butyl	Ph-	7-(N)-morpholine
	22	iso-butyl	Ph-	7-(N)-azetidine
	23	iso-butyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	iso-butyl	Ph-	7-(N)-pyrrolidine
	25	iso-butyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	iso-butyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	iso-butyl	Ph-	7-(N)-N'-methylpiperazine
	28	iso-butyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	iso-butyl	Ph-	7-NH-CBZ
	30	iso-butyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	iso-butyl	Ph-	7-NHC(O)CH ₂ Br
	32	iso-butyl	Ph-	7-NH-C(NH)NH ₂
	33	iso-butyl	Ph-	7-(2)-thiophene
	34	iso-butyl	Ph-	8-methyl
	35	iso-butyl	Ph-	8-ethyl
	36	iso-butyl	Ph-	8-iso-propyl
	37	iso-butyl	Ph-	8-tert-butyl
	38	iso-butyl	Ph-	8-OH
	39	iso-butyl	Ph-	8-OCH ₃
	40	iso-butyl	Ph-	8-O(iso-propyl)
	41	iso-butyl	Ph-	8-SCH ₃
	42	iso-butyl	Ph-	8-SOCH ₃
	43	iso-butyl	Ph-	8-SO ₂ CH ₃
	44	iso-butyl	Ph-	8-SCH ₂ CH ₃

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	45	iso-butyl	Ph-	8-NH ₂
	46	iso-butyl	Ph-	8-NHOH
	47	iso-butyl	Ph-	8-NHCH ₃
	48	iso-butyl	Ph-	8-N(CH ₃) ₂
	49	iso-butyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	iso-butyl	Ph-	8-NHC(=O)CH ₃
	51	iso-butyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	iso-butyl	Ph-	8-NMeCH ₂ CO ₂ H
	53	iso-butyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	iso-butyl	Ph-	8-(N)-morpholine
	55	iso-butyl	Ph-	8-(N)-azetidine
	56	iso-butyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	iso-butyl	Ph-	8-(N)-pyrrolidine
	58	iso-butyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	iso-butyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	iso-butyl	Ph-	8-(N)-N'-methylpiperazine
	61	iso-butyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	iso-butyl	Ph-	8-NH-CBZ
	63	iso-butyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	iso-butyl	Ph-	8-NHC(O)CH ₂ Br
	65	iso-butyl	Ph-	8-NH-C(NH)NH ₂
	66	iso-butyl	Ph-	8-(2)-thiophene
	67	iso-butyl	Ph-	9-methyl
	68	iso-butyl	Ph-	9-ethyl
	69	iso-butyl	Ph-	9-iso-propyl
	70	iso-butyl	Ph-	9-tert-butyl
	71	iso-butyl	Ph-	9-OH
	72	iso-butyl	Ph-	9-OCH ₃
	73	iso-butyl	Ph-	9-O(iso-propyl)
	74	iso-butyl	Ph-	9-SCH ₃
	75	iso-butyl	Ph-	9-SOCH ₃
	76	iso-butyl	Ph-	9-SO ₂ CH ₃
	77	iso-butyl	Ph-	9-SCH ₂ CH ₃
	78	iso-butyl	Ph-	9-NH ₂
	79	iso-butyl	Ph-	9-NHOH
	80	iso-butyl	Ph-	9-NHCH ₃
	81	iso-butyl	Ph-	9-N(CH ₃) ₂

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	82	iso-butyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	iso-butyl	Ph-	9-NHC(=O)CH ₃
	84	iso-butyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	iso-butyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	iso-butyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	iso-butyl	Ph-	9-(N)-morpholine
	88	iso-butyl	Ph-	9-(N)-azetidine
	89	iso-butyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	iso-butyl	Ph-	9-(N)-pyrrolidine
	91	iso-butyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	iso-butyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	iso-butyl	Ph-	9-(N)-N'-methylpiperazine
	93	iso-butyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	iso-butyl	Ph-	9-NH-CBZ
	96	iso-butyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	iso-butyl	Ph-	9-NHC(O)CH ₂ Br
	98	iso-butyl	Ph-	9-NH-C(NH)NH ₂
	99	iso-butyl	Ph-	9-(2)-thiophene
	100	iso-butyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	iso-butyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	iso-butyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	iso-butyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.008	01	iso-pentyl	Ph-	7-methyl
	02	iso-pentyl	Ph-	7-ethyl
	03	iso-pentyl	Ph-	7-iso-propyl
	04	iso-pentyl	Ph-	7-tert-butyl
	05	iso-pentyl	Ph-	7-OH
	06	iso-pentyl	Ph-	7-OCH ₃
	07	iso-pentyl	Ph-	7-O(iso-propyl)
	08	iso-pentyl	Ph-	7-SCH ₃
	09	iso-pentyl	Ph-	7-SOCH ₃
	10	iso-pentyl	Ph-	7-SO ₂ CH ₃
	11	iso-pentyl	Ph-	7-SCH ₂ CH ₃
	12	iso-pentyl	Ph-	7-NH ₂
	13	iso-pentyl	Ph-	7-NHOH
	14	iso-pentyl	Ph-	7-NHCH ₃
	15	iso-pentyl	Ph-	7-N(CH ₃) ₂

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	16	iso-pentyl	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	iso-pentyl	Ph-	7-NHC(=O)CH ₃
	18	iso-pentyl	Ph-	7-N(CH ₂ CH ₃) ₂
	19	iso-pentyl	Ph-	7-NMeCH ₂ CO ₂ H
	20	iso-pentyl	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	iso-pentyl	Ph-	7-(N)-morpholine
	22	iso-pentyl	Ph-	7-(N)-azetidine
	23	iso-pentyl	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	iso-pentyl	Ph-	7-(N)-pyrrolidine
	25	iso-pentyl	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	iso-pentyl	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	iso-pentyl	Ph-	7-(N)-N'-methylpiperazine
	28	iso-pentyl	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	iso-pentyl	Ph-	7-NH-CBZ
	30	iso-pentyl	Ph-	7-NHC(O)C ₅ H ₁₁
	31	iso-pentyl	Ph-	7-NHC(O)CH ₂ Br
	32	iso-pentyl	Ph-	7-NH-C(NH)NH ₂
	33	iso-pentyl	Ph-	7-(2)-thiophene
	34	iso-pentyl	Ph-	8-methyl
	35	iso-pentyl	Ph-	8-ethyl
	36	iso-pentyl	Ph-	8-iso-propyl
	37	iso-pentyl	Ph-	8-tert-butyl
	38	iso-pentyl	Ph-	8-OH
	39	iso-pentyl	Ph-	8-OCH ₃
	40	iso-pentyl	Ph-	8-O(iso-propyl)
	41	iso-pentyl	Ph-	8-SCH ₃
	42	iso-pentyl	Ph-	8-SOCH ₃
	43	iso-pentyl	Ph-	8-SO ₂ CH ₃
	44	iso-pentyl	Ph-	8-SCH ₂ CH ₃
	45	iso-pentyl	Ph-	8-NH ₂
	46	iso-pentyl	Ph-	8-NHOH
	47	iso-pentyl	Ph-	8-NHCH ₃
	48	iso-pentyl	Ph-	8-N(CH ₃) ₂
	49	iso-pentyl	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	iso-pentyl	Ph-	8-NHC(=O)CH ₃
	51	iso-pentyl	Ph-	8-N(CH ₂ CH ₃) ₂
	52	iso-pentyl	Ph-	8-NMeCH ₂ CO ₂ H

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	53	iso-pentyl	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	iso-pentyl	Ph-	8-(N)-morpholine
	55	iso-pentyl	Ph-	8-(N)-azetidine
	56	iso-pentyl	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	iso-pentyl	Ph-	8-(N)-pyrrolidine
	58	iso-pentyl	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	iso-pentyl	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	iso-pentyl	Ph-	8-(N)-N'-methylpiperazine
	61	iso-pentyl	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	iso-pentyl	Ph-	8-NH-CBZ
	63	iso-pentyl	Ph-	8-NHC(O)C ₅ H ₁₁
	64	iso-pentyl	Ph-	8-NHC(O)CH ₂ Br
	65	iso-pentyl	Ph-	8-NH-C(NH)NH ₂
	66	iso-pentyl	Ph-	8-(2)-thiophene
	67	iso-pentyl	Ph-	9-methyl
	68	iso-pentyl	Ph-	9-ethyl
	69	iso-pentyl	Ph-	9-iso-propyl
	70	iso-pentyl	Ph-	9-tert-butyl
	71	iso-pentyl	Ph-	9-OH
	72	iso-pentyl	Ph-	9-OCH ₃
	73	iso-pentyl	Ph-	9-O(iso-propyl)
	74	iso-pentyl	Ph-	9-SCH ₃
	75	iso-pentyl	Ph-	9-SOCH ₃
	76	iso-pentyl	Ph-	9-SO ₂ CH ₃
	77	iso-pentyl	Ph-	9-SCH ₂ CH ₃
	78	iso-pentyl	Ph-	9-NH ₂
	79	iso-pentyl	Ph-	9-NHOH
	80	iso-pentyl	Ph-	9-NHCH ₃
	81	iso-pentyl	Ph-	9-N(CH ₃) ₂
	82	iso-pentyl	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	iso-pentyl	Ph-	9-NHC(=O)CH ₃
	84	iso-pentyl	Ph-	9-N(CH ₂ CH ₃) ₂
	85	iso-pentyl	Ph-	9-NMeCH ₂ CO ₂ H
	86	iso-pentyl	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	iso-pentyl	Ph-	9-(N)-morpholine
	88	iso-pentyl	Ph-	9-(N)-azetidine
	89	iso-pentyl	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	iso-pentyl	Ph-	9-(N)-pyrrolidine

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	91	iso-pentyl	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	iso-pentyl	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	iso-pentyl	Ph-	9-(N)-N'-methylpiperazine
	93	iso-pentyl	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	iso-pentyl	Ph-	9-NH-CBZ
	96	iso-pentyl	Ph-	9-NHC(O)C ₅ H ₁₁
	97	iso-pentyl	Ph-	9-NHC(O)CH ₂ Br
	98	iso-pentyl	Ph-	9-NH-C(NH)NH ₂
	99	iso-pentyl	Ph-	9-(2)-thiophene
	100	iso-pentyl	Ph-	7-OCH ₃ , 8-OCH ₃
	101	iso-pentyl	Ph-	7-SCH ₃ , 8-OCH ₃
	102	iso-pentyl	Ph-	7-SCH ₃ , 8-SCH ₃
	103	iso-pentyl	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.009	01	CH ₂ C(=O)C ₂ H ₅	Ph-	7-methyl
	02	CH ₂ C(=O)C ₂ H ₅	Ph-	7-ethyl
	03	CH ₂ C(=O)C ₂ H ₅	Ph-	7-iso-propyl
	04	CH ₂ C(=O)C ₂ H ₅	Ph-	7-tert-butyl
	05	CH ₂ C(=O)C ₂ H ₅	Ph-	7-OH
	06	CH ₂ C(=O)C ₂ H ₅	Ph-	7-OCH ₃
	07	CH ₂ C(=O)C ₂ H ₅	Ph-	7-O(iso-propyl)
	08	CH ₂ C(=O)C ₂ H ₅	Ph-	7-SCH ₃
	09	CH ₂ C(=O)C ₂ H ₅	Ph-	7-SOCH ₃
	10	CH ₂ C(=O)C ₂ H ₅	Ph-	7-SO ₂ CH ₃
	11	CH ₂ C(=O)C ₂ H ₅	Ph-	7-SCH ₂ CH ₃
	12	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NH ₂
	13	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NHOH
	14	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NHCH ₃
	15	CH ₂ C(=O)C ₂ H ₅	Ph-	7-N(CH ₃) ₂
	16	CH ₂ C(=O)C ₂ H ₅	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NHC(=O)CH ₃
	18	CH ₂ C(=O)C ₂ H ₅	Ph-	7-N(CH ₂ CH ₃) ₂
	19	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NMeCH ₂ CO ₂ H
	20	CH ₂ C(=O)C ₂ H ₅	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-morpholine
	22	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-azetidine
	23	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-N-methylazetidinium, I ⁻

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	24	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-pyrrolidine
	25	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-N'-methylpiperazine
	28	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NH-CBZ
	30	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NHC(O)C ₅ H ₁₁
	31	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NHC(O)CH ₂ Br
	32	CH ₂ C(=O)C ₂ H ₅	Ph-	7-NH-C(NH)NH ₂
	33	CH ₂ C(=O)C ₂ H ₅	Ph-	7-(2)-thiophene
	34	CH ₂ C(=O)C ₂ H ₅	Ph-	8-methyl
	35	CH ₂ C(=O)C ₂ H ₅	Ph-	8-ethyl
	36	CH ₂ C(=O)C ₂ H ₅	Ph-	8-iso-propyl
	37	CH ₂ C(=O)C ₂ H ₅	Ph-	8-tert-butyl
	38	CH ₂ C(=O)C ₂ H ₅	Ph-	8-OH
	39	CH ₂ C(=O)C ₂ H ₅	Ph-	8-OCH ₃
	40	CH ₂ C(=O)C ₂ H ₅	Ph-	8-O(iso-propyl)
	41	CH ₂ C(=O)C ₂ H ₅	Ph-	8-SCH ₃
	42	CH ₂ C(=O)C ₂ H ₅	Ph-	8-SOCH ₃
	43	CH ₂ C(=O)C ₂ H ₅	Ph-	8-SO ₂ CH ₃
	44	CH ₂ C(=O)C ₂ H ₅	Ph-	8-SCH ₂ CH ₃
	45	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NH ₂
	46	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NHOH
	47	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NHCH ₃
	48	CH ₂ C(=O)C ₂ H ₅	Ph-	8-N(CH ₃) ₂
	49	CH ₂ C(=O)C ₂ H ₅	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NHC(=O)CH ₃
	51	CH ₂ C(=O)C ₂ H ₅	Ph-	8-N(CH ₂ CH ₃) ₂
	52	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NMeCH ₂ CO ₂ H
	53	CH ₂ C(=O)C ₂ H ₅	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-morpholine
	55	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-azetidine
	56	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-pyrrolidine
	58	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-N-methyl-morpholinium, I ⁻

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	60	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-N'-methylpiperazine
	61	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NH-CBZ
	63	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NHC(O)C ₅ H ₁₁
	64	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NHC(O)CH ₂ Br
	65	CH ₂ C(=O)C ₂ H ₅	Ph-	8-NH-C(NH)NH ₂
	66	CH ₂ C(=O)C ₂ H ₅	Ph-	8-(2)-thiophene
	67	CH ₂ C(=O)C ₂ H ₅	Ph-	9-methyl
	68	CH ₂ C(=O)C ₂ H ₅	Ph-	9-ethyl
	69	CH ₂ C(=O)C ₂ H ₅	Ph-	9-iso-propyl
	70	CH ₂ C(=O)C ₂ H ₅	Ph-	9-tert-butyl
	71	CH ₂ C(=O)C ₂ H ₅	Ph-	9-OH
	72	CH ₂ C(=O)C ₂ H ₅	Ph-	9-OCH ₃
	73	CH ₂ C(=O)C ₂ H ₅	Ph-	9-O(iso-propyl)
	74	CH ₂ C(=O)C ₂ H ₅	Ph-	9-SCH ₃
	75	CH ₂ C(=O)C ₂ H ₅	Ph-	9-SOCH ₃
	76	CH ₂ C(=O)C ₂ H ₅	Ph-	9-SO ₂ CH ₃
	77	CH ₂ C(=O)C ₂ H ₅	Ph-	9-SCH ₂ CH ₃
	78	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NH ₂
	79	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NHOH
	80	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NHCH ₃
	81	CH ₂ C(=O)C ₂ H ₅	Ph-	9-N(CH ₃) ₂
	82	CH ₂ C(=O)C ₂ H ₅	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NHC(=O)CH ₃
	84	CH ₂ C(=O)C ₂ H ₅	Ph-	9-N(CH ₂ CH ₃) ₂
	85	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NMeCH ₂ CO ₂ H
	86	CH ₂ C(=O)C ₂ H ₅	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-morpholine
	88	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-azetidine
	89	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-pyrrolidine
	91	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-N'-methylpiperazine
	93	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NH-CBZ

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	96	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NHC(O)C ₅ H ₁₁
	97	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NHC(O)CH ₂ Br
	98	CH ₂ C(=O)C ₂ H ₅	Ph-	9-NH-C(NH)NH ₂
	99	CH ₂ C(=O)C ₂ H ₅	Ph-	9-(2)-thiophene
	100	CH ₂ C(=O)C ₂ H ₅	Ph-	7-OCH ₃ , 8-OCH ₃
	101	CH ₂ C(=O)C ₂ H ₅	Ph-	7-SCH ₃ , 8-OCH ₃
	102	CH ₂ C(=O)C ₂ H ₅	Ph-	7-SCH ₃ , 8-SCH ₃
	103	CH ₂ C(=O)C ₂ H ₅	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.010	01	CH ₂ OC ₂ H ₅	Ph-	7-methyl
	02	CH ₂ OC ₂ H ₅	Ph-	7-ethyl
	03	CH ₂ OC ₂ H ₅	Ph-	7-iso-propyl
	04	CH ₂ OC ₂ H ₅	Ph-	7-tert-butyl
	05	CH ₂ OC ₂ H ₅	Ph-	7-OH
	06	CH ₂ OC ₂ H ₅	Ph-	7-OCH ₃
	07	CH ₂ OC ₂ H ₅	Ph-	7-O(iso-propyl)
	08	CH ₂ OC ₂ H ₅	Ph-	7-SCH ₃
	09	CH ₂ OC ₂ H ₅	Ph-	7-SOCH ₃
	10	CH ₂ OC ₂ H ₅	Ph-	7-SO ₂ CH ₃
	11	CH ₂ OC ₂ H ₅	Ph-	7-SCH ₂ CH ₃
	12	CH ₂ OC ₂ H ₅	Ph-	7-NH ₂
	13	CH ₂ OC ₂ H ₅	Ph-	7-NHOH
	14	CH ₂ OC ₂ H ₅	Ph-	7-NHCH ₃
	15	CH ₂ OC ₂ H ₅	Ph-	7-N(CH ₃) ₂
	16	CH ₂ OC ₂ H ₅	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	CH ₂ OC ₂ H ₅	Ph-	7-NHC(=O)CH ₃
	18	CH ₂ OC ₂ H ₅	Ph-	7-N(CH ₂ CH ₃) ₂
	19	CH ₂ OC ₂ H ₅	Ph-	7-NMeCH ₂ CO ₂ H
	20	CH ₂ OC ₂ H ₅	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	CH ₂ OC ₂ H ₅	Ph-	7-(N)-morpholine
	22	CH ₂ OC ₂ H ₅	Ph-	7-(N)-azetidine
	23	CH ₂ OC ₂ H ₅	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	CH ₂ OC ₂ H ₅	Ph-	7-(N)-pyrrolidine
	25	CH ₂ OC ₂ H ₅	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	CH ₂ OC ₂ H ₅	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	CH ₂ OC ₂ H ₅	Ph-	7-(N)-N'-methylpiperazine
	28	CH ₂ OC ₂ H ₅	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	29	CH ₂ OC ₂ H ₅	Ph-	7-NH-CBZ
	30	CH ₂ OC ₂ H ₅	Ph-	7-NHC(O)C ₅ H ₁₁
	31	CH ₂ OC ₂ H ₅	Ph-	7-NHC(O)CH ₂ Br
	32	CH ₂ OC ₂ H ₅	Ph-	7-NH-C(NH)NH ₂
	33	CH ₂ OC ₂ H ₅	Ph-	7-(2)-thiophene
	34	CH ₂ OC ₂ H ₅	Ph-	8-methyl
	35	CH ₂ OC ₂ H ₅	Ph-	8-ethyl
	36	CH ₂ OC ₂ H ₅	Ph-	8-iso-propyl
	37	CH ₂ OC ₂ H ₅	Ph-	8-tert-butyl
	38	CH ₂ OC ₂ H ₅	Ph-	8-OH
	39	CH ₂ OC ₂ H ₅	Ph-	8-OCH ₃
	40	CH ₂ OC ₂ H ₅	Ph-	8-O(iso-propyl)
	41	CH ₂ OC ₂ H ₅	Ph-	8-SCH ₃
	42	CH ₂ OC ₂ H ₅	Ph-	8-SOCH ₃
	43	CH ₂ OC ₂ H ₅	Ph-	8-SO ₂ CH ₃
	44	CH ₂ OC ₂ H ₅	Ph-	8-SCH ₂ CH ₃
	45	CH ₂ OC ₂ H ₅	Ph-	8-NH ₂
	46	CH ₂ OC ₂ H ₅	Ph-	8-NHOH
	47	CH ₂ OC ₂ H ₅	Ph-	8-NHCH ₃
	48	CH ₂ OC ₂ H ₅	Ph-	8-N(CH ₃) ₂
	49	CH ₂ OC ₂ H ₅	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	CH ₂ OC ₂ H ₅	Ph-	8-NHC(=O)CH ₃
	51	CH ₂ OC ₂ H ₅	Ph-	8-N(CH ₂ CH ₃) ₂
	52	CH ₂ OC ₂ H ₅	Ph-	8-NMeCH ₂ CO ₂ H
	53	CH ₂ OC ₂ H ₅	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	CH ₂ OC ₂ H ₅	Ph-	8-(N)-morpholine
	55	CH ₂ OC ₂ H ₅	Ph-	8-(N)-azetidine
	56	CH ₂ OC ₂ H ₅	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	CH ₂ OC ₂ H ₅	Ph-	8-(N)-pyrrolidine
	58	CH ₂ OC ₂ H ₅	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	CH ₂ OC ₂ H ₅	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	CH ₂ OC ₂ H ₅	Ph-	8-(N)-N'-methylpiperazine
	61	CH ₂ OC ₂ H ₅	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	CH ₂ OC ₂ H ₅	Ph-	8-NH-CBZ
	63	CH ₂ OC ₂ H ₅	Ph-	8-NHC(O)C ₅ H ₁₁
	64	CH ₂ OC ₂ H ₅	Ph-	8-NHC(O)CH ₂ Br

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	65	CH ₂ OC ₂ H ₅	Ph-	8-NH-C(NH)NH ₂
	66	CH ₂ OC ₂ H ₅	Ph-	8-(2)-thiophene
	67	CH ₂ OC ₂ H ₅	Ph-	9-methyl
	68	CH ₂ OC ₂ H ₅	Ph-	9-ethyl
	69	CH ₂ OC ₂ H ₅	Ph-	9-iso-propyl
	70	CH ₂ OC ₂ H ₅	Ph-	9-tert-butyl
	71	CH ₂ OC ₂ H ₅	Ph-	9-OH
	72	CH ₂ OC ₂ H ₅	Ph-	9-OCH ₃
	73	CH ₂ OC ₂ H ₅	Ph-	9-O(iso-propyl)
	74	CH ₂ OC ₂ H ₅	Ph-	9-SCH ₃
	75	CH ₂ OC ₂ H ₅	Ph-	9-SOCH ₃
	76	CH ₂ OC ₂ H ₅	Ph-	9-SO ₂ CH ₃
	77	CH ₂ OC ₂ H ₅	Ph-	9-SCH ₂ CH ₃
	78	CH ₂ OC ₂ H ₅	Ph-	9-NH ₂
	79	CH ₂ OC ₂ H ₅	Ph-	9-NHOH
	80	CH ₂ OC ₂ H ₅	Ph-	9-NHCH ₃
	81	CH ₂ OC ₂ H ₅	Ph-	9-N(CH ₃) ₂
	82	CH ₂ OC ₂ H ₅	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	CH ₂ OC ₂ H ₅	Ph-	9-NHC(=O)CH ₃
	84	CH ₂ OC ₂ H ₅	Ph-	9-N(CH ₂ CH ₃) ₂
	85	CH ₂ OC ₂ H ₅	Ph-	9-NMeCH ₂ CO ₂ H
	86	CH ₂ OC ₂ H ₅	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	CH ₂ OC ₂ H ₅	Ph-	9-(N)-morpholine
	88	CH ₂ OC ₂ H ₅	Ph-	9-(N)-azetidine
	89	CH ₂ OC ₂ H ₅	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	CH ₂ OC ₂ H ₅	Ph-	9-(N)-pyrrolidine
	91	CH ₂ OC ₂ H ₅	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	CH ₂ OC ₂ H ₅	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	CH ₂ OC ₂ H ₅	Ph-	9-(N)-N'-methylpiperazine
	93	CH ₂ OC ₂ H ₅	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	CH ₂ OC ₂ H ₅	Ph-	9-NH-CBZ
	96	CH ₂ OC ₂ H ₅	Ph-	9-NHC(O)C ₅ H ₁₁
	97	CH ₂ OC ₂ H ₅	Ph-	9-NHC(O)CH ₂ Br
	98	CH ₂ OC ₂ H ₅	Ph-	9-NH-C(NH)NH ₂
	99	CH ₂ OC ₂ H ₅	Ph-	9-(2)-thiophene

Prefix (FFF.xxx)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	100	CH ₂ OC ₂ H ₅	Ph-	7-OCH ₃ , 8-OCH ₃
	101	CH ₂ OC ₂ H ₅	Ph-	7-SCH ₃ , 8-OCH ₃
	102	CH ₂ OC ₂ H ₅	Ph-	7-SCH ₃ , 8-SCH ₃
	103	CH ₂ OC ₂ H ₅	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.011	01	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-methyl
	02	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-ethyl
	03	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-iso-propyl
	04	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-tert-butyl
	05	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-OH
	06	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-OCH ₃
	07	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-O(iso-propyl)
	08	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-SCH ₃
	09	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-SOCH ₃
	10	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-SO ₂ CH ₃
	11	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-SCH ₂ CH ₃
	12	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NH ₂
	13	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NHOH
	14	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NHCH ₃
	15	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-N(CH ₃) ₂
	16	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NHC(=O)CH ₃
	18	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-N(CH ₂ CH ₃) ₂
	19	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NMeCH ₂ CO ₂ H
	20	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-morpholine
	22	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-azetidine
	23	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-pyrrolidine
	25	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-N'-methylpiperazine
	28	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NH-CBZ
	30	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NHC(O)C ₅ H ₁₁
	31	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NHC(O)CH ₂ Br
	32	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-NH-C(NH)NH ₂
	33	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-(2)-thiophene

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	34	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-methyl
	35	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-ethyl
	36	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-iso-propyl
	37	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-tert-butyl
	38	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-OH
	39	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-OCH ₃
	40	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-O(iso-propyl)
	41	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-SCH ₃
	42	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-SOCH ₃
	43	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-SO ₂ CH ₃
	44	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-SCH ₂ CH ₃
	45	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NH ₂
	46	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NHOH
	47	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NHCH ₃
	48	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-N(CH ₃) ₂
	49	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NHC(=O)CH ₃
	51	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-N(CH ₂ CH ₃) ₂
	52	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NMeCH ₂ CO ₂ H
	53	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-morpholine
	55	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-azetidine
	56	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-pyrrolidine
	58	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-N'-methylpiperazine
	61	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NH-CBZ
	63	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NHC(O)C ₅ H ₁₁
	64	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NHC(O)CH ₂ Br
	65	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-NH-C(NH)NH ₂
	66	CH ₂ CH(OH)C ₂ H ₅	Ph-	8-(2)-thiophene
	67	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-methyl
	68	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-ethyl

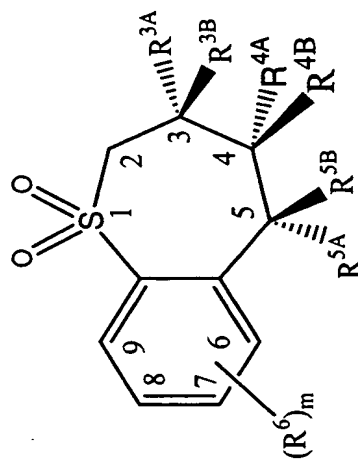
Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	69	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-iso-propyl
	70	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-tert-butyl
	71	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-OH
	72	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-OCH ₃
	73	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-O(iso-propyl)
	74	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-SCH ₃
	75	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-SOCH ₃
	76	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-SO ₂ CH ₃
	77	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-SCH ₂ CH ₃
	78	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NH ₂
	79	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NHOH
	80	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NHCH ₃
	81	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-N(CH ₃) ₂
	82	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NHC(=O)CH ₃
	84	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-N(CH ₂ CH ₃) ₂
	85	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NMeCH ₂ CO ₂ H
	86	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-morpholine
	88	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-azetidine
	89	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-pyrrolidine
	91	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-N'-methylpiperazine
	93	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NH-CBZ
	96	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NHC(O)C ₅ H ₁₁
	97	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NHC(O)CH ₂ Br
	98	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-NH-C(NH)NH ₂
	99	CH ₂ CH(OH)C ₂ H ₅	Ph-	9-(2)-thiophene
	100	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-OCH ₃ , 8-OCH ₃
	101	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-SCH ₃ , 8-OCH ₃
	102	CH ₂ CH(OH)C ₂ H ₅	Ph-	7-SCH ₃ , 8-SCH ₃
	103	CH ₂ CH(OH)C ₂ H ₅	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃
F101.012	01	CH ₂ O-(4-picoline)	Ph-	7-methyl

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	02	CH ₂ O-(4-picoline)	Ph-	7-ethyl
	03	CH ₂ O-(4-picoline)	Ph-	7-iso-propyl
	04	CH ₂ O-(4-picoline)	Ph-	7-tert-butyl
	05	CH ₂ O-(4-picoline)	Ph-	7-OH
	06	CH ₂ O-(4-picoline)	Ph-	7-OCH ₃
	07	CH ₂ O-(4-picoline)	Ph-	7-O(iso-propyl)
	08	CH ₂ O-(4-picoline)	Ph-	7-SCH ₃
	09	CH ₂ O-(4-picoline)	Ph-	7-SOCH ₃
	10	CH ₂ O-(4-picoline)	Ph-	7-SO ₂ CH ₃
	11	CH ₂ O-(4-picoline)	Ph-	7-SCH ₂ CH ₃
	12	CH ₂ O-(4-picoline)	Ph-	7-NH ₂
	13	CH ₂ O-(4-picoline)	Ph-	7-NHOH
	14	CH ₂ O-(4-picoline)	Ph-	7-NHCH ₃
	15	CH ₂ O-(4-picoline)	Ph-	7-N(CH ₃) ₂
	16	CH ₂ O-(4-picoline)	Ph-	7-N ⁺ (CH ₃) ₃ , I ⁻
	17	CH ₂ O-(4-picoline)	Ph-	7-NHC(=O)CH ₃
	18	CH ₂ O-(4-picoline)	Ph-	7-N(CH ₂ CH ₃) ₂
	19	CH ₂ O-(4-picoline)	Ph-	7-NMeCH ₂ CO ₂ H
	20	CH ₂ O-(4-picoline)	Ph-	7-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	21	CH ₂ O-(4-picoline)	Ph-	7-(N)-morpholine
	22	CH ₂ O-(4-picoline)	Ph-	7-(N)-azetidine
	23	CH ₂ O-(4-picoline)	Ph-	7-(N)-N-methylazetidinium, I ⁻
	24	CH ₂ O-(4-picoline)	Ph-	7-(N)-pyrrolidine
	25	CH ₂ O-(4-picoline)	Ph-	7-(N)-N-methyl-pyrrolidinium, I ⁻
	26	CH ₂ O-(4-picoline)	Ph-	7-(N)-N-methyl-morpholinium, I ⁻
	27	CH ₂ O-(4-picoline)	Ph-	7-(N)-N'-methylpiperazine
	28	CH ₂ O-(4-picoline)	Ph-	7-(N)-N'-dimethylpiperazinium, I ⁻
	29	CH ₂ O-(4-picoline)	Ph-	7-NH-CBZ
	30	CH ₂ O-(4-picoline)	Ph-	7-NHC(O)C ₅ H ₁₁
	31	CH ₂ O-(4-picoline)	Ph-	7-NHC(O)CH ₂ Br
	32	CH ₂ O-(4-picoline)	Ph-	7-NH-C(NH)NH ₂
	33	CH ₂ O-(4-picoline)	Ph-	7-(2)-thiophene
	34	CH ₂ O-(4-picoline)	Ph-	8-methyl
	35	CH ₂ O-(4-picoline)	Ph-	8-ethyl
	36	CH ₂ O-(4-picoline)	Ph-	8-iso-propyl
	37	CH ₂ O-(4-picoline)	Ph-	8-tert-butyl

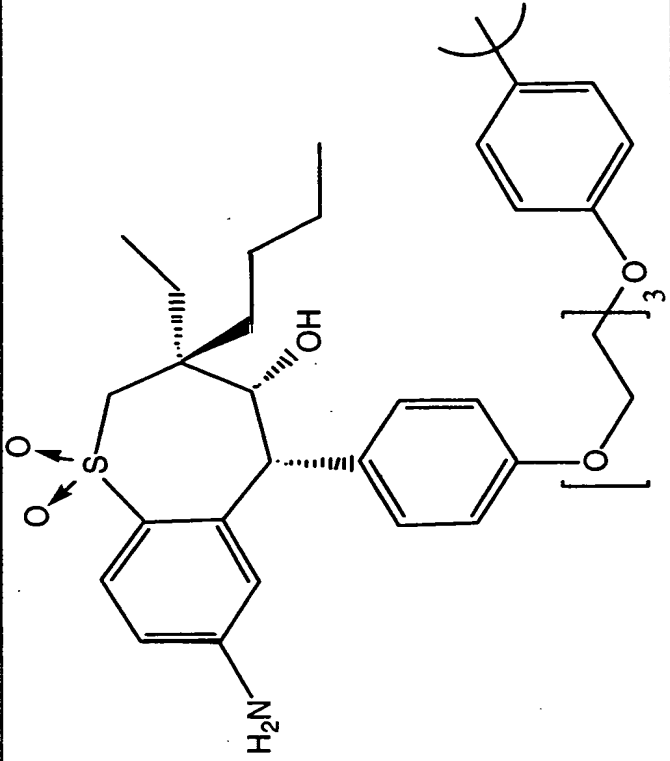
Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	38	CH ₂ O-(4-picoline)	Ph-	8-OH
	39	CH ₂ O-(4-picoline)	Ph-	8-OCH ₃
	40	CH ₂ O-(4-picoline)	Ph-	8-O(iso-propyl)
	41	CH ₂ O-(4-picoline)	Ph-	8-SCH ₃
	42	CH ₂ O-(4-picoline)	Ph-	8-SOCH ₃
	43	CH ₂ O-(4-picoline)	Ph-	8-SO ₂ CH ₃
	44	CH ₂ O-(4-picoline)	Ph-	8-SCH ₂ CH ₃
	45	CH ₂ O-(4-picoline)	Ph-	8-NH ₂
	46	CH ₂ O-(4-picoline)	Ph-	8-NHOH
	47	CH ₂ O-(4-picoline)	Ph-	8-NHCH ₃
	48	CH ₂ O-(4-picoline)	Ph-	8-N(CH ₃) ₂
	49	CH ₂ O-(4-picoline)	Ph-	8-N ⁺ (CH ₃) ₃ , I ⁻
	50	CH ₂ O-(4-picoline)	Ph-	8-NHC(=O)CH ₃
	51	CH ₂ O-(4-picoline)	Ph-	8-N(CH ₂ CH ₃) ₂
	52	CH ₂ O-(4-picoline)	Ph-	8-NMeCH ₂ CO ₂ H
	53	CH ₂ O-(4-picoline)	Ph-	8-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	54	CH ₂ O-(4-picoline)	Ph-	8-(N)-morpholine
	55	CH ₂ O-(4-picoline)	Ph-	8-(N)-azetidine
	56	CH ₂ O-(4-picoline)	Ph-	8-(N)-N-methylazetidinium, I ⁻
	57	CH ₂ O-(4-picoline)	Ph-	8-(N)-pyrrolidine
	58	CH ₂ O-(4-picoline)	Ph-	8-(N)-N-methyl-pyrrolidinium, I ⁻
	59	CH ₂ O-(4-picoline)	Ph-	8-(N)-N-methyl-morpholinium, I ⁻
	60	CH ₂ O-(4-picoline)	Ph-	8-(N)-N'-methylpiperazine
	61	CH ₂ O-(4-picoline)	Ph-	8-(N)-N'-dimethylpiperazinium, I ⁻
	62	CH ₂ O-(4-picoline)	Ph-	8-NH-CBZ
	63	CH ₂ O-(4-picoline)	Ph-	8-NHC(O)C ₅ H ₁₁
	64	CH ₂ O-(4-picoline)	Ph-	8-NHC(O)CH ₂ Br
	65	CH ₂ O-(4-picoline)	Ph-	8-NH-C(NH)NH ₂
	66	CH ₂ O-(4-picoline)	Ph-	8-(2)-thiophene
	67	CH ₂ O-(4-picoline)	Ph-	9-methyl
	68	CH ₂ O-(4-picoline)	Ph-	9-ethyl
	69	CH ₂ O-(4-picoline)	Ph-	9-iso-propyl
	70	CH ₂ O-(4-picoline)	Ph-	9-tert-butyl
	71	CH ₂ O-(4-picoline)	Ph-	9-OH
	72	CH ₂ O-(4-picoline)	Ph-	9-OCH ₃
	73	CH ₂ O-(4-picoline)	Ph-	9-O(iso-propyl)

Prefix (FFF.xxx.)	Cpd# yyy)	R ^{3A} = R ^{3B}	R ^{5A}	(R ⁶) _m
	74	CH ₂ O-(4-picoline)	Ph-	9-SCH ₃
	75	CH ₂ O-(4-picoline)	Ph-	9-SOCH ₃
	76	CH ₂ O-(4-picoline)	Ph-	9-SO ₂ CH ₃
	77	CH ₂ O-(4-picoline)	Ph-	9-SCH ₂ CH ₃
	78	CH ₂ O-(4-picoline)	Ph-	9-NH ₂
	79	CH ₂ O-(4-picoline)	Ph-	9-NHOH
	80	CH ₂ O-(4-picoline)	Ph-	9-NHCH ₃
	81	CH ₂ O-(4-picoline)	Ph-	9-N(CH ₃) ₂
	82	CH ₂ O-(4-picoline)	Ph-	9-N ⁺ (CH ₃) ₃ , I ⁻
	83	CH ₂ O-(4-picoline)	Ph-	9-NHC(=O)CH ₃
	84	CH ₂ O-(4-picoline)	Ph-	9-N(CH ₂ CH ₃) ₂
	85	CH ₂ O-(4-picoline)	Ph-	9-NMeCH ₂ CO ₂ H
	86	CH ₂ O-(4-picoline)	Ph-	9-N ⁺ (Me) ₂ CH ₂ CO ₂ H, I ⁻
	87	CH ₂ O-(4-picoline)	Ph-	9-(N)-morpholine
	88	CH ₂ O-(4-picoline)	Ph-	9-(N)-azetidine
	89	CH ₂ O-(4-picoline)	Ph-	9-(N)-N-methylazetidinium, I ⁻
	90	CH ₂ O-(4-picoline)	Ph-	9-(N)-pyrrolidine
	91	CH ₂ O-(4-picoline)	Ph-	9-(N)-N-methyl-pyrrolidinium, I ⁻
	92	CH ₂ O-(4-picoline)	Ph-	9-(N)-N-methyl-morpholinium, I ⁻
	93	CH ₂ O-(4-picoline)	Ph-	9-(N)-N'-methylpiperazine
	93	CH ₂ O-(4-picoline)	Ph-	9-(N)-N'-dimethylpiperazinium, I ⁻
	95	CH ₂ O-(4-picoline)	Ph-	9-NH-CBZ
	96	CH ₂ O-(4-picoline)	Ph-	9-NHC(O)C ₅ H ₁₁
	97	CH ₂ O-(4-picoline)	Ph-	9-NHC(O)CH ₂ Br
	98	CH ₂ O-(4-picoline)	Ph-	9-NH-C(NH)NH ₂
	99	CH ₂ O-(4-picoline)	Ph-	9-(2)-thiophene
	100	CH ₂ O-(4-picoline)	Ph-	7-OCH ₃ , 8-OCH ₃
	101	CH ₂ O-(4-picoline)	Ph-	7-SCH ₃ , 8-OCH ₃
	102	CH ₂ O-(4-picoline)	Ph-	7-SCH ₃ , 8-SCH ₃
	103	CH ₂ O-(4-picoline)	Ph-	6-OCH ₃ , 7-OCH ₃ , 8-OCH ₃

Table 6

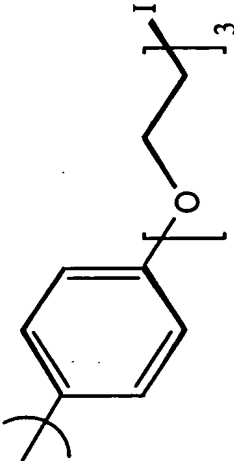
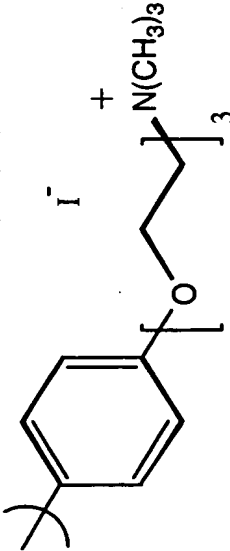
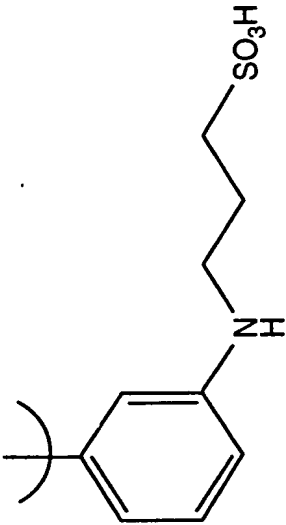


Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
101	ethyl	n-butyl	OH	H	phenyl
102	ethyl	n-butyl	OH	H	phenyl
103	n-butyl	Ethyl	OH	H	phenyl
104	ethyl	n-butyl	OH	H	phenyl
105	ethyl	n-butyl	OH	H	phenyl
106	ethyl	n-butyl	OH	H	phenyl
107	n-butyl	Ethyl	OH	H	4-(decyloxy)phenyl
108	ethyl	n-butyl	OH	H	phenyl
109	ethyl	n-butyl	OH	H	4-(decyloxy)phenyl
110	ethyl	n-butyl	OH	H	phenyl
111	n-butyl	Ethyl	OH	H	4-hydroxyphenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
112	ethyl	n-butyl	OH	H	
113	ethyl	n-butyl	OH	H	4-hydroxyphenyl
114	ethyl	n-butyl	OH	H	4-methoxyphenyl
115	n-butyl	ethyl	OH	H	4-methoxyphenyl
116	ethyl	n-butyl	OH	H	4-methoxyphenyl
117	n-butyl	ethyl	OH	H	phenyl
118	ethyl	n-butyl	OH	H	phenyl
119	ethyl	n-butyl	OH	H	phenyl
120	n-butyl	ethyl	OH	H	phenyl
121	ethyl	n-butyl	OH	H	phenyl

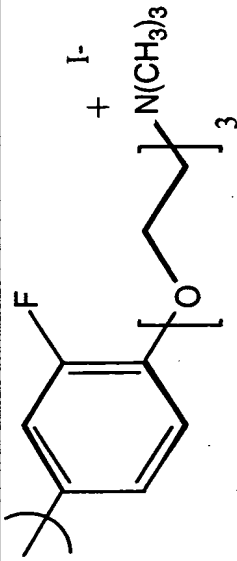
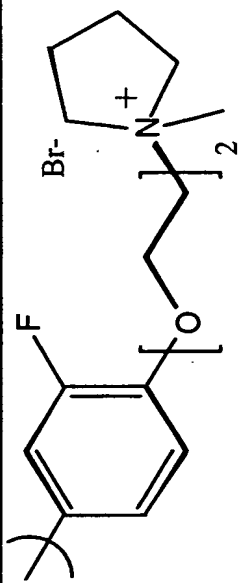
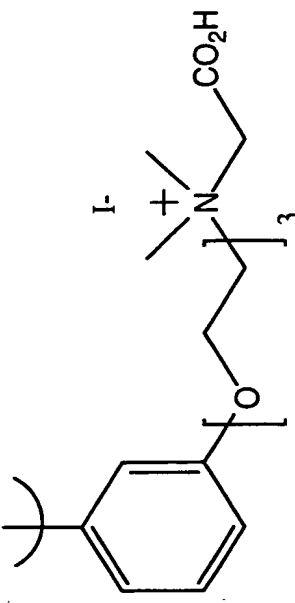
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
122	n-butyl	ethyl	OH	H	phenyl
123	ethyl	n-butyl	OH	H	phenyl
124	n-butyl	ethyl	OH	H	phenyl
125	ethyl	n-butyl	OH	H	phenyl
126	n-butyl	ethyl	OH	H	4-fluorophenyl
127	n-butyl	ethyl	OH	H	4-fluorophenyl
128	Ethyl	n-butyl	OH	H	4-fluorophenyl
129	Ethyl	n-butyl	OH	H	4-fluorophenyl
131	Ethyl	n-butyl	OH	H	4-fluorophenyl
132	Ethyl	n-butyl	OH	H	phenyl
133	Ethyl	n-butyl	OH	H	phenyl
134	Ethyl	n-butyl	OH	H	phenyl
135	Ethyl	n-butyl	OH	H	phenyl
136	Ethyl	n-butyl	OH	H	phenyl
137	n-butyl	ethyl	OH	H	phenyl
138	n-butyl	ethyl	OH	H	phenyl
139	n-butyl	ethyl	OH	H	phenyl
140					
141					
142	Ethyl	n-butyl	H	OH	H
143	Ethyl	n-butyl	OH	H	3-methoxyphenyl
144	Ethyl	n-butyl	OH	H	4-fluorophenyl
262	Ethyl	n-butyl	OH	H	3-methoxyphenyl
263	Ethyl	n-butyl	H	OH	H
264	Ethyl	n-butyl	OH	H	3-trifluoromethylphenyl
265	Ethyl	n-butyl	H	OH	H

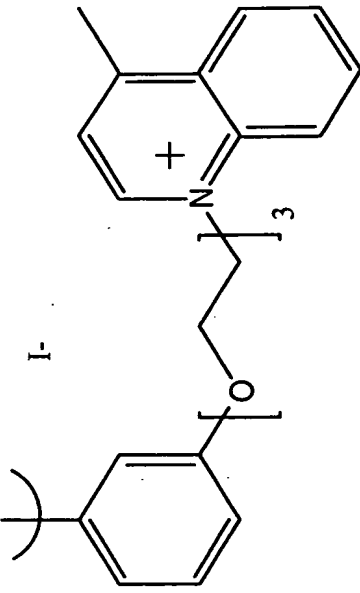
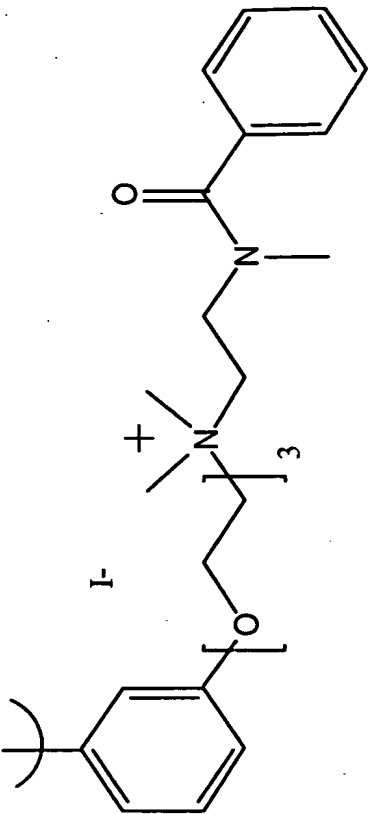
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
266	Ethyl	n-butyl	OH	H	3-hydroxyphenyl
267	Ethyl	n-butyl	OH	H	3-hydroxyphenyl
268	Ethyl	n-butyl	OH	H	4-fluorophenyl
269	Ethyl	n-butyl	H	OH	H
270	Ethyl	n-butyl	OH	H	4-fluorophenyl
271	Ethyl	n-butyl	OH	H	3-methoxyphenyl
272	Ethyl	n-butyl	H	OH	H
273	Ethyl	n-butyl	H	OH	H
274	Ethyl	n-butyl	OH	H	4-fluorophenyl
275	Ethyl	n-butyl	H	OH	H
276	Ethyl	n-butyl	OH	H	3-methoxyphenyl
277	Ethyl	n-butyl	OH	H	3-fluorophenyl
278	Ethyl	n-butyl	H	OH	2-fluorophenyl
279	Ethyl	n-butyl	H	OH	3-fluorophenyl
280	Ethyl	n-butyl	OH	H	2-fluorophenyl
281	Ethyl	n-butyl	OH	H	4-fluorophenyl
282	Ethyl	n-butyl	OH	H	4-fluorophenyl
283	Ethyl	n-butyl	H	OH	H
284	Ethyl	n-butyl	OH	H	4-fluorophenyl
286	Ethyl	ethyl	OH	H	phenyl
287	Ethyl	ethyl	OH	H	phenyl
288	methyl	methyl	OH	H	phenyl
289	n-butyl	n-butyl	OH	H	phenyl
290	n-butyl	n-butyl	OH	H	phenyl
291	n-butyl	n-butyl	OH	H	phenyl
292	n-butyl	n-butyl	OH	H	4-fluorophenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
293	n-butyl	n-butyl	OH	H	phenyl
294	n-butyl	n-butyl	OH	H	phenyl
295	Ethyl	n-butyl	OH	H	
296	Ethyl	n-butyl	OH	H	
1000	Ethyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1001	Ethyl	n-butyl	OH	H	
1002	Ethyl	n-butyl	OH	H	
1003	Ethyl	n-butyl	OH	H	

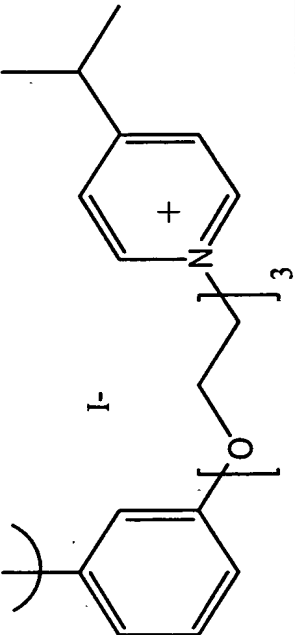
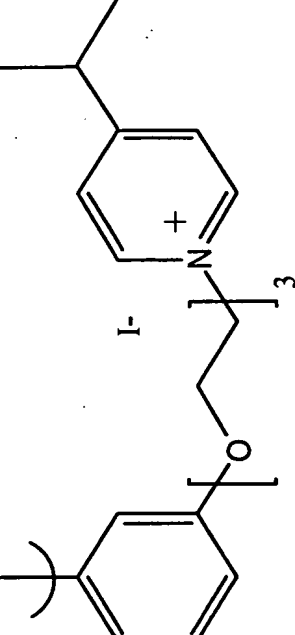
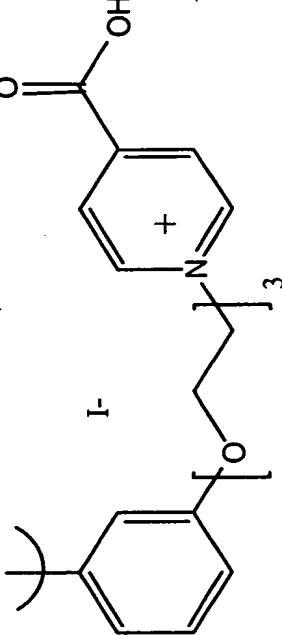
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1007	n-butyl	n-butyl	OH	H	
1008	n-butyl	n-butyl	OH	H	
1009	n-butyl	n-butyl	OH	H	
1010	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl

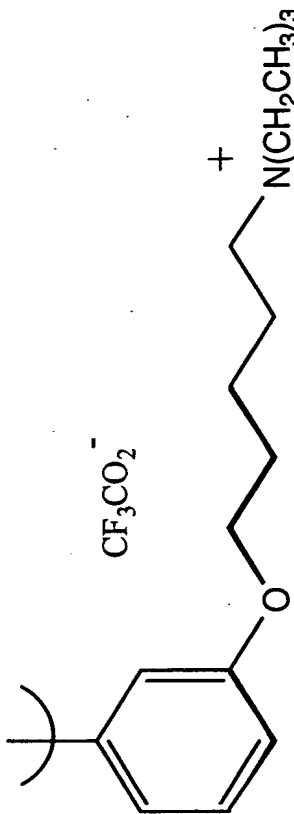
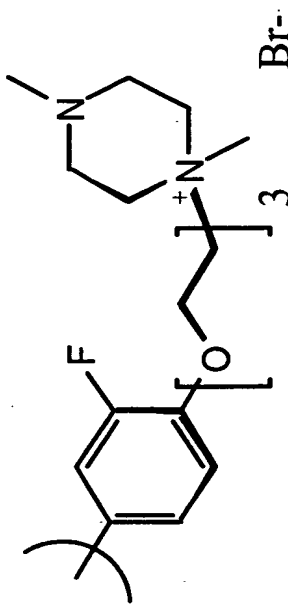
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1011	n-butyl	n-butyl	OH	H	3-fluoro-4-(5-triethylammoniumpentyl)oxyphenyl, trifluoroacetate salt
1012	n-butyl	n-butyl	OH	H	4-hydroxyphenyl
1013	n-butyl	n-butyl	OH	H	
1014	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1015	n-butyl	n-butyl	OH	H	
1016	n-butyl	n-butyl	OH	H	

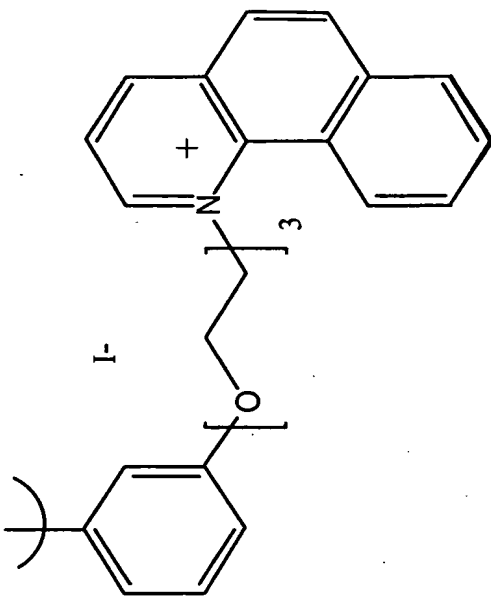
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1017	n-butyl	n-butyl	OH	H	
1018	n-butyl	n-butyl	OH	H	

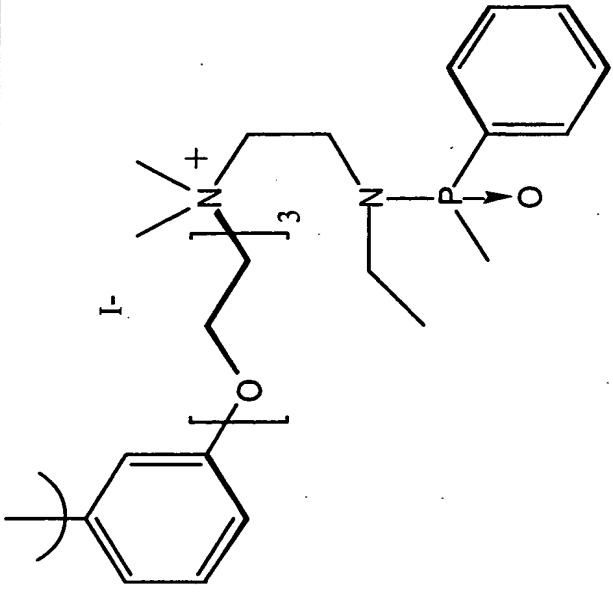
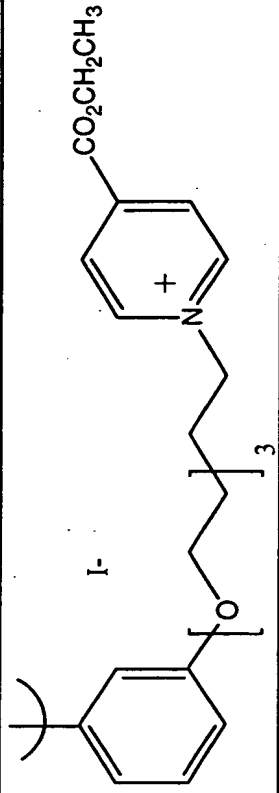
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1022	n-butyl	n-butyl	OH	H	
1023	n-butyl	n-butyl	OH	H	

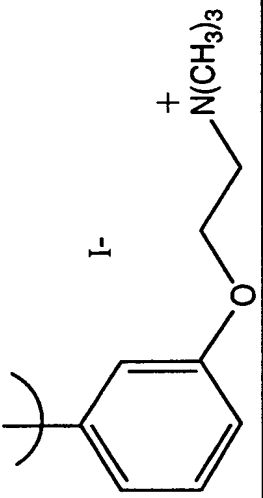

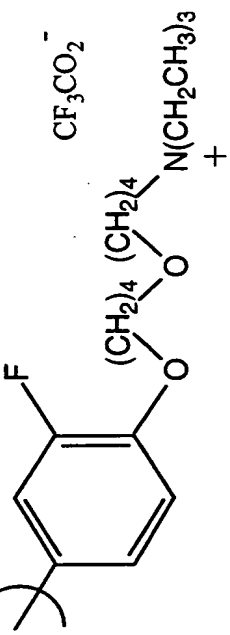
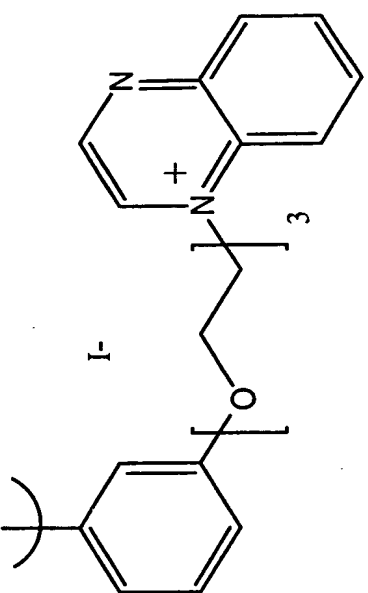
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1024	n-butyl	n-butyl	OH	H	
1025	n-butyl	n-butyl	OH	H	

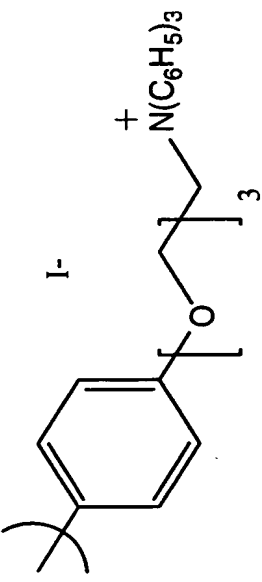
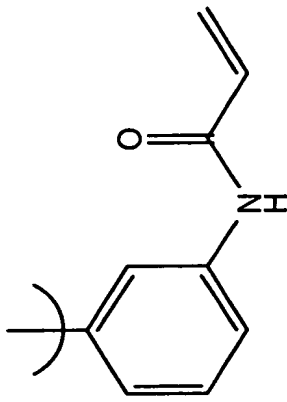
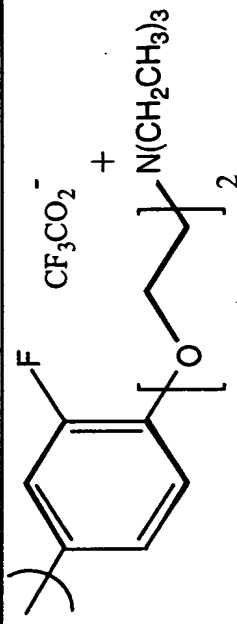
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1026	n-butyl	n-butyl	OH	H	
1027	n-butyl	n-butyl	OH	H	
1028	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1032	n-butyl	n-butyl	OH	H	
1033	n-butyl	n-butyl	OH	H	

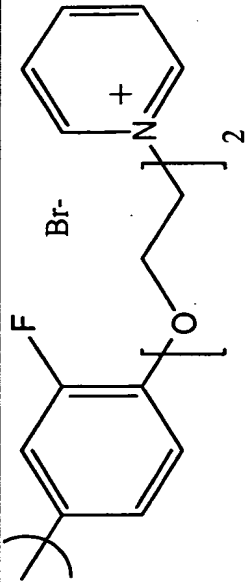
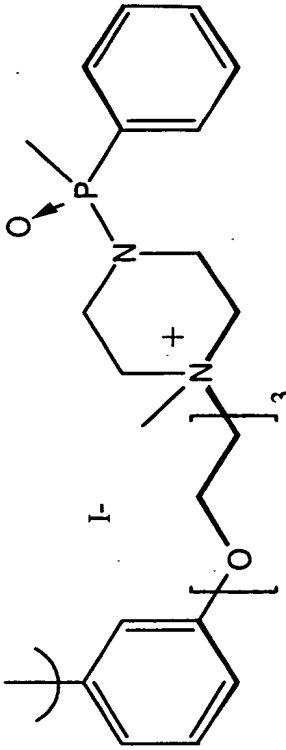
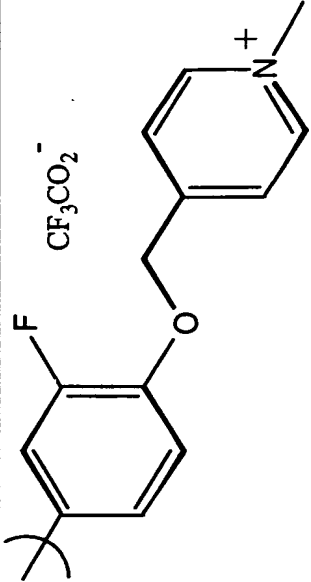
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1034	n-butyl	n-butyl	OH	H	

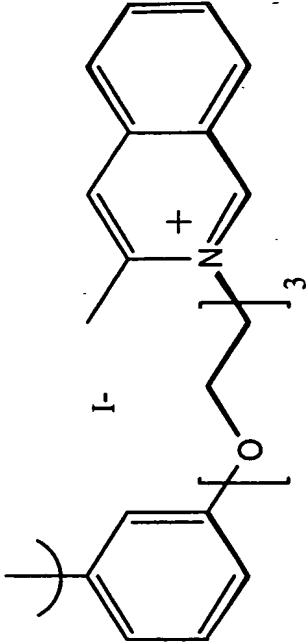
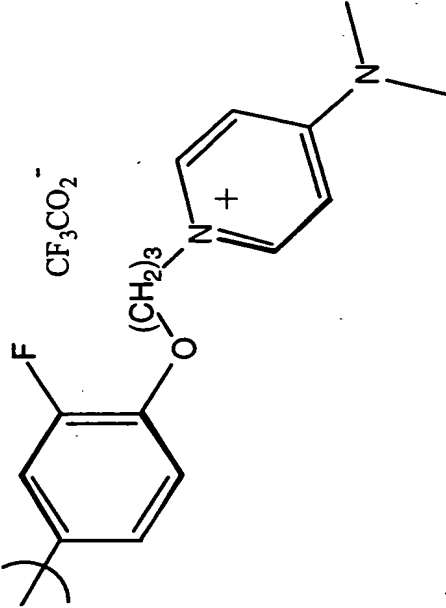
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1035	n-butyl	n-butyl	OH	H	
1036	n-butyl	n-butyl	OH	H	
1037	n-butyl	n-butyl	OH	H	4-hydroxyphenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1038	n-butyl	n-butyl	OH	H	
1039	n-butyl	n-butyl	OH	H	
1040	n-butyl	n-butyl	OH	H	
1041	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1042	n-butyl	n-butyl	OH	H	
1043	n-butyl	n-butyl	OH	H	
1044	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1045	n-butyl	n-butyl	OH	H	
1046	n-butyl	n-butyl	OH	H	3-aminophenyl
1047	n-butyl	n-butyl	OH	H	
1048	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1049	n-butyl	n-butyl	OH	H	
1050	n-butyl	n-butyl	OH	H	
1051	n-butyl	n-butyl	OH	H	

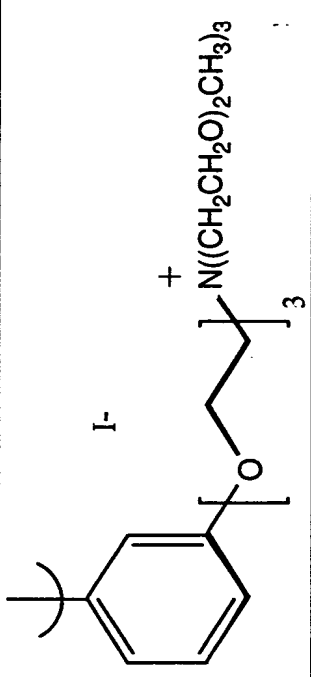
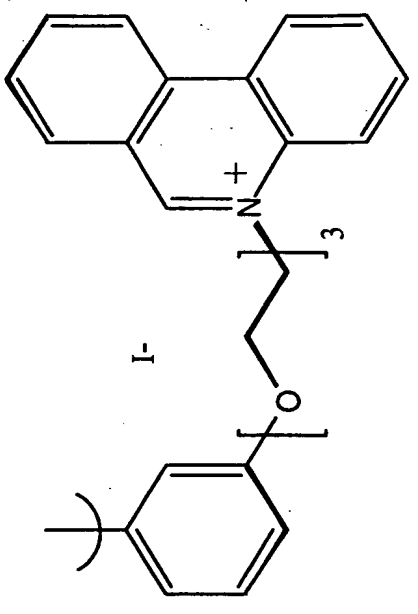
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1052	n-butyl	n-butyl	OH	H	
1053	n-butyl	n-butyl	OH	H	

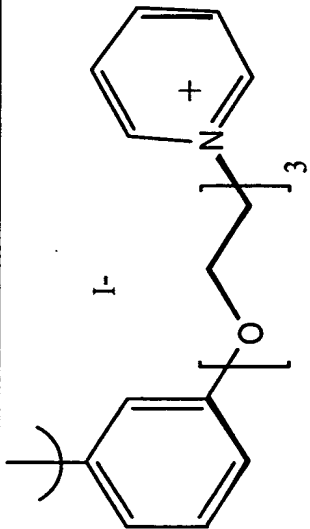
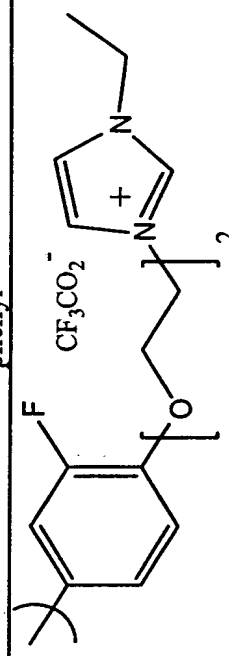
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1054	n-butyl	n-butyl	OH	H	
1055	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1056	n-butyl	n-butyl	OH	H	
1057	n-butyl	n-butyl	OH	H	
1058	n-butyl	n-butyl	OH	H	

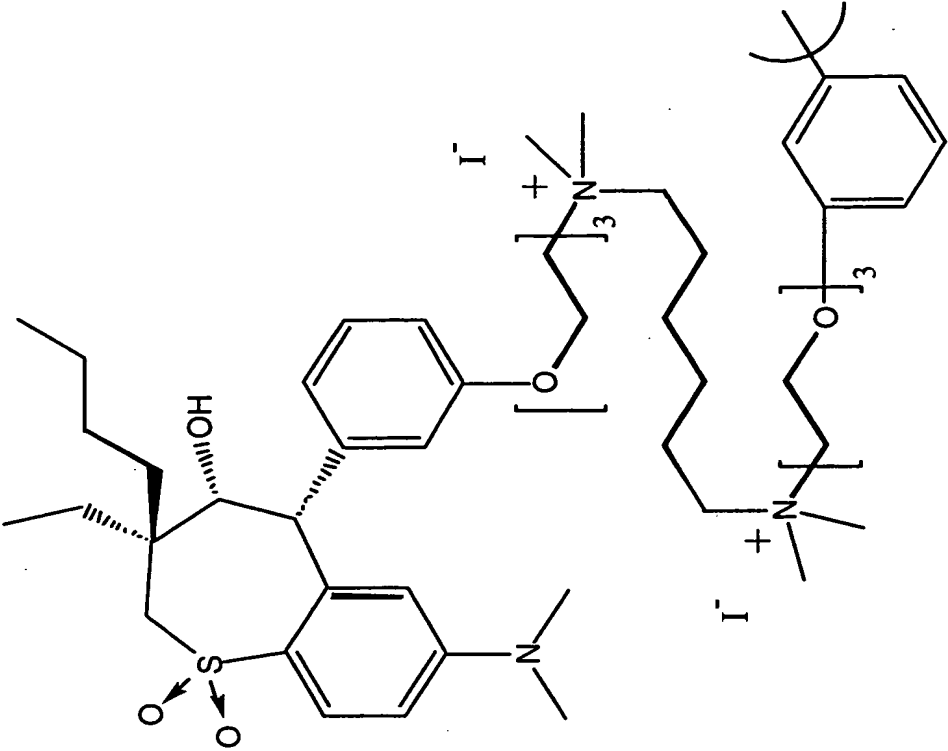
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1059	n-butyl	n-butyl	OH	H	
1060	Ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1061	n-butyl	n-butyl	OH	H	
1062	n-butyl	n-butyl	OH	H	

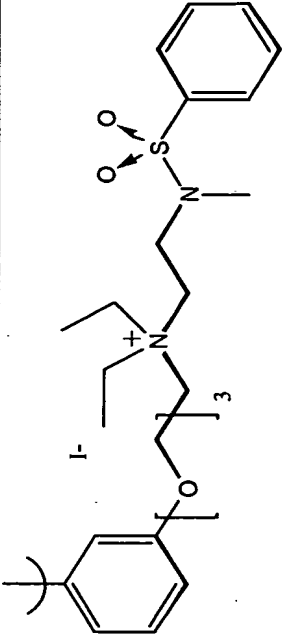
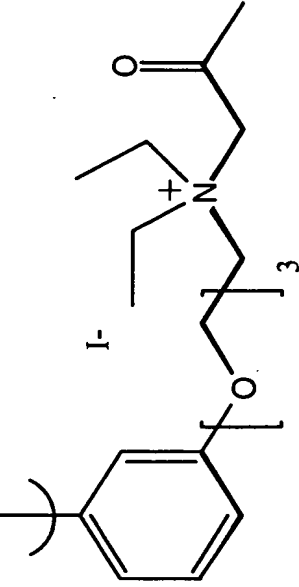
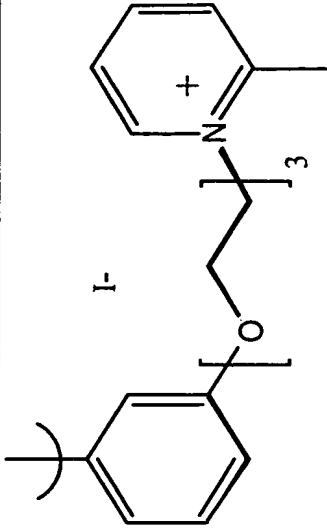
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1063	n-butyl	n-butyl	OH	H	
1064	n-butyl	n-butyl	OH	H	

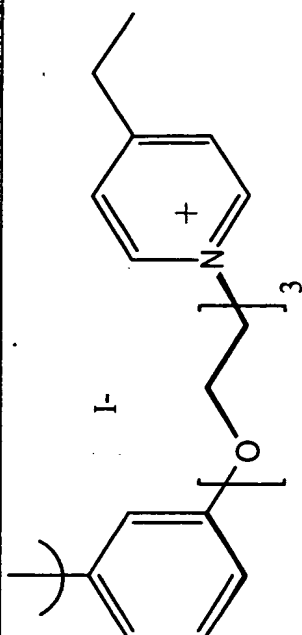
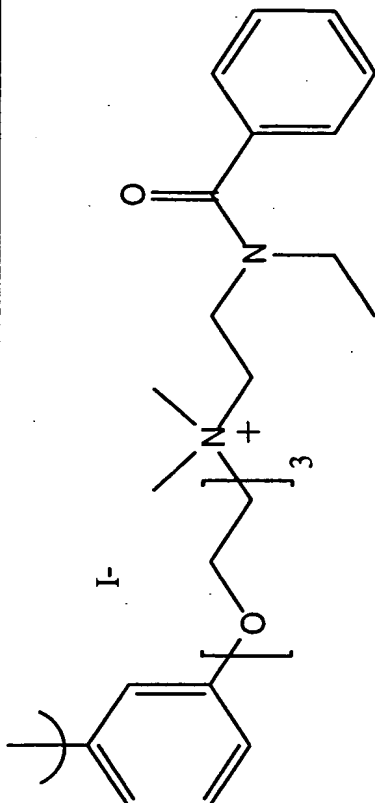
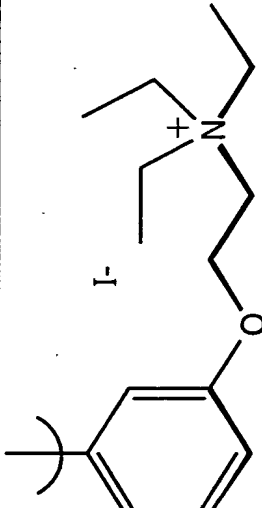
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1065	n-butyl	n-butyl	OH	H	
1066	n-butyl	n-butyl	OH	H	
1067	n-butyl	n-butyl	OH	H	thiophen-3-yl

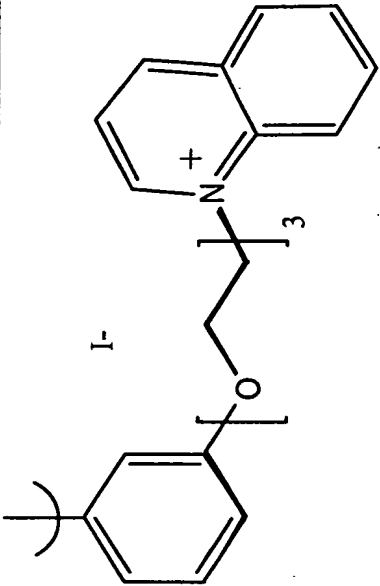
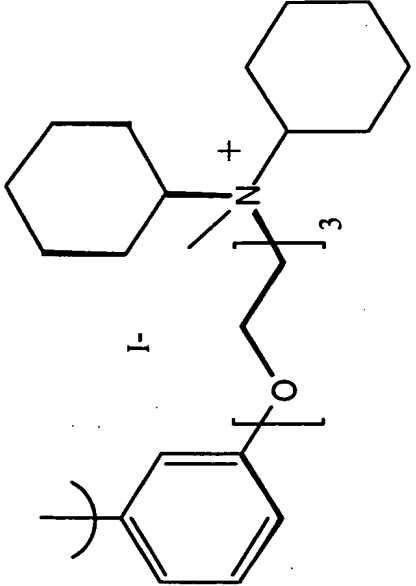
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{SA}
1068	n-butyl	n-butyl	OH	H	
1069	n-butyl	n-butyl	OH	H	phenyl
1070	n-butyl	n-butyl	OH	H	

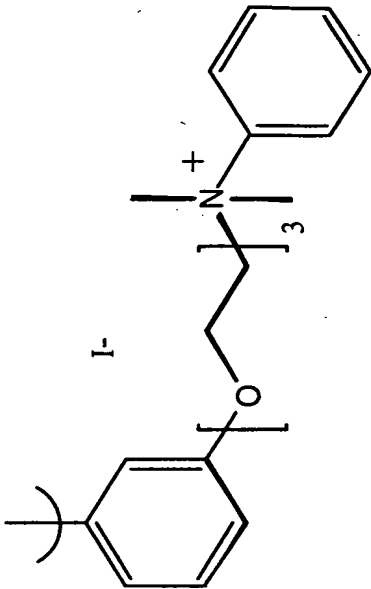
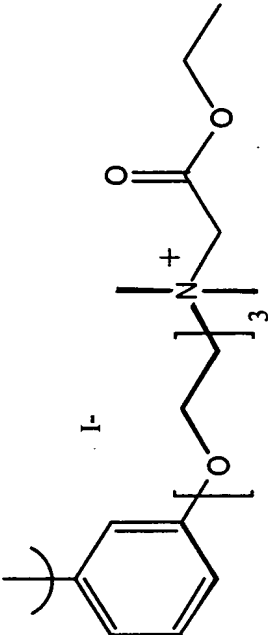
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1071	n-butyl	n-butyl	OH	H	<p>The structure shows a poly(4-phenyleneoxy) chain, represented by a benzene ring with a vertical line at the top and a horizontal line at the bottom, connected to an oxygen atom which is part of a repeating unit with a subscript 3. The chain is terminated by a triethylammonium cation (N⁺ with three ethyl groups) and an iodide anion (I⁻). A dimethylphenylphosphonium group is also attached to the chain, consisting of a phosphorus atom double-bonded to an oxygen atom and single-bonded to two methyl groups and a phenyl ring.</p>
1072	n-butyl	n-butyl	OH	H	<p>The structure shows a poly(4-phenyleneoxy) chain, represented by a benzene ring with a vertical line at the top and a horizontal line at the bottom, connected to an oxygen atom which is part of a repeating unit with a subscript 3. The chain is terminated by a 4-(hydroxymethyl)pyridinium cation (N⁺ with a methyl group and a 4-(hydroxymethyl)phenyl group) and an iodide anion (I⁻). A dimethylphenylphosphonium group is also attached to the chain, consisting of a phosphorus atom double-bonded to an oxygen atom and single-bonded to two methyl groups and a phenyl ring.</p>

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1079	Ethyl	n-butyl	OH	H	

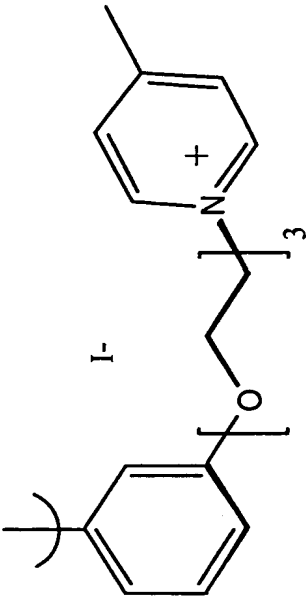
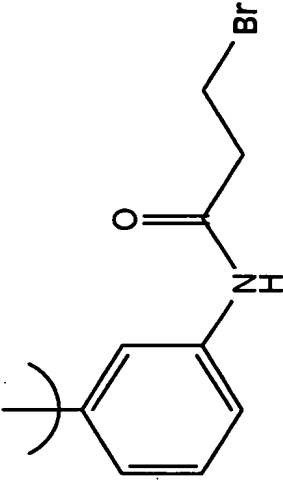
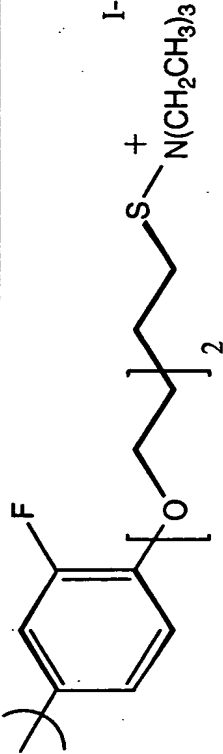
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1080	n-butyl	n-butyl	OH	H	
1081	n-butyl	n-butyl	OH	H	
1082	n-butyl	n-butyl	OH	H	2-pyridyl
1083	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1084	n-butyl	n-butyl	OH	H	
1085	n-butyl	n-butyl	OH	H	thiophen-3-yl
1086	n-butyl	n-butyl	OH	H	
1087	n-butyl	n-butyl	OH	H	

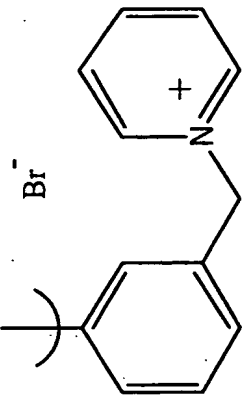
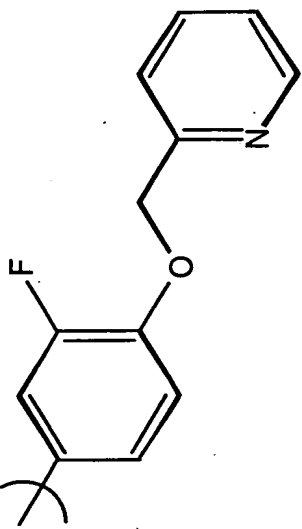
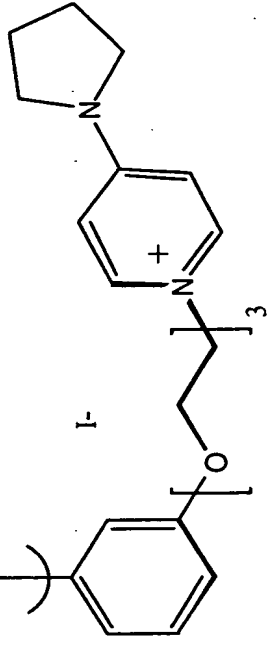
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1088	Ethyl	n-butyl	OH	H	3,4-methylenedioxyphenyl
1089	Ethyl	n-butyl	OH	H	4-methoxyphenyl
1090	n-butyl	n-butyl	OH	H	
1091	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1092	n-butyl	n-butyl	OH	H	
1093	n-butyl	n-butyl	OH	H	

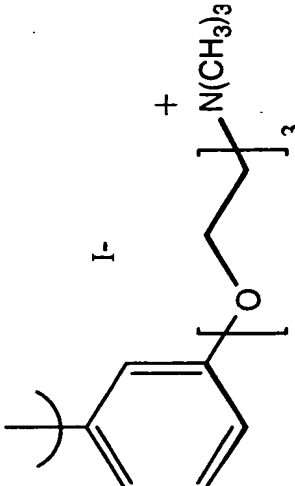
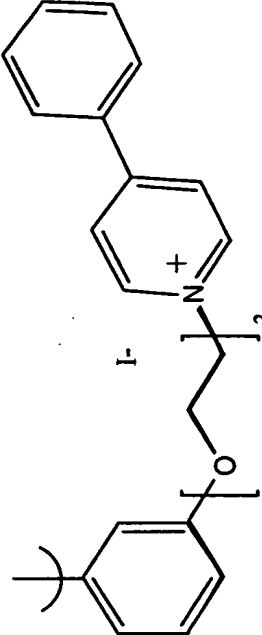
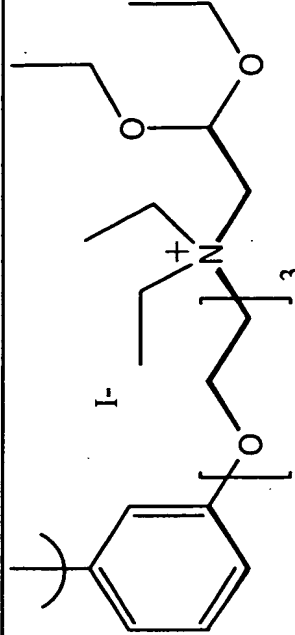
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1094	n-butyl	n-butyl	OH	H	
1095	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1096	n-butyl	n-butyl	OH	H	
1097	n-butyl	n-butyl	OH	H	
1098	n-butyl	n-butyl	OH	H	
1099	Ethyl	n-butyl	OH	H	4-methoxyphenyl
1100	n-butyl	n-butyl	OH	H	4-methoxyphenyl

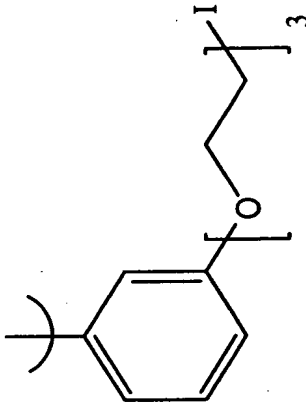
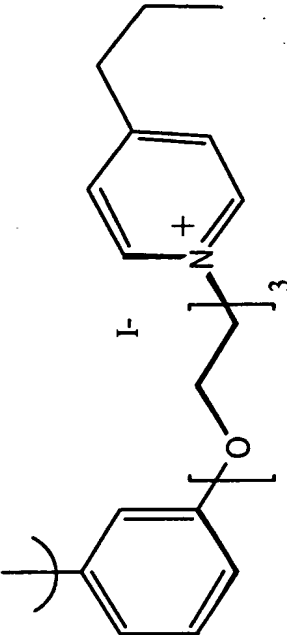
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1101	n-butyl	n-butyl	OH	H	
1102	n-butyl	n-butyl	OH	H	3-carboxymethylphenyl
1103	n-butyl	n-butyl	OH	H	
1104	n-butyl	n-butyl	OH	H	
1105	n-butyl	n-butyl	OH	H	5-piperonyl

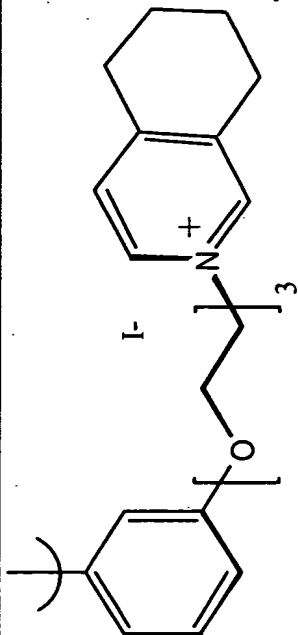
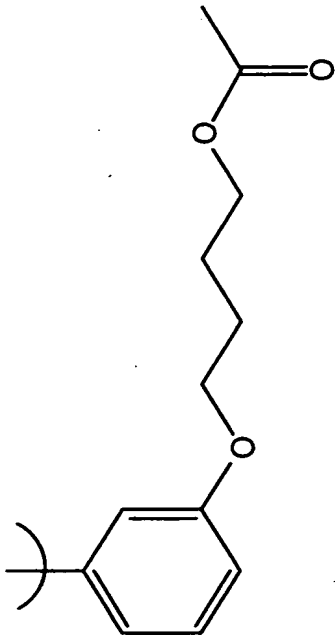
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1106	n-butyl	n-butyl	OH	H	3-hydroxyphenyl
1107	n-butyl	n-butyl	OH	H	
1108	n-butyl	n-butyl	OH	H	3-pyridyl
1109	n-butyl	n-butyl	OH	H	
1110	n-butyl	n-butyl	OH	H	

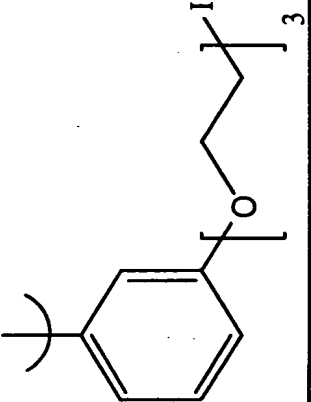
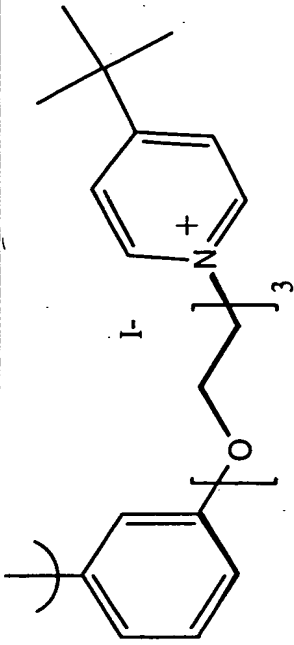
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1111	n-butyl	n-butyl	OH	H	
1112	n-butyl	n-butyl	OH	H	4-pyridyl
1113	n-butyl	n-butyl	OH	H	
1114	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1115	n-butyl	n-butyl	OH	H	4-fluorophenyl
1116	Ethyl	n-butyl	OH	H	3-tolyl

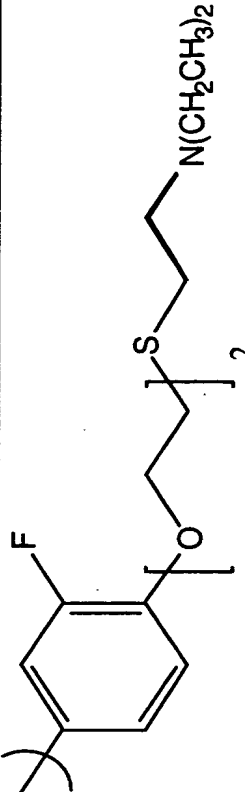
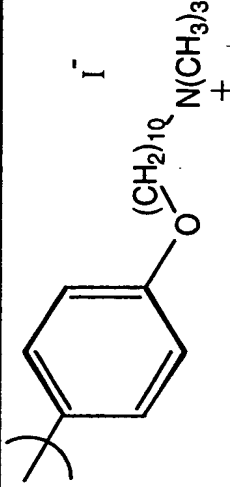
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1117	Ethyl	n-butyl	OH	H	
1118	Ethyl	n-butyl	OH	H	3-fluoro-4-hydroxyphenyl
1119	n-butyl	n-butyl	OH	H	
1120	n-butyl	n-butyl	OH	H	

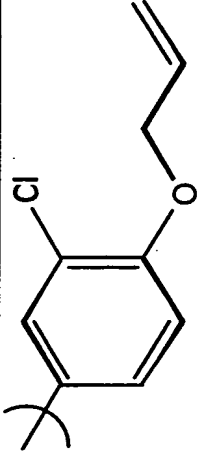
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1121	n-butyl	n-butyl	OH	H	
1122	n-butyl	n-butyl	OH	H	
1123	n-butyl	n-butyl	OH	H	phenyl
1124	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1125	n-butyl	n-butyl	OH	H	3-chloro-4-methoxyphenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1126	Ethyl	n-butyl	OH	H	
1127	n-butyl	n-butyl	OH	H	
1128	n-butyl	n-butyl	OH	H	3-fluoro-4-hydroxyphenyl
1129	n-butyl	n-butyl	OH	H	4-fluorophenyl
1130	n-butyl	n-butyl	OH	H	3-chloro-4-fluorophenyl
1131	Ethyl	n-butyl	OH	H	4-methoxyphenyl

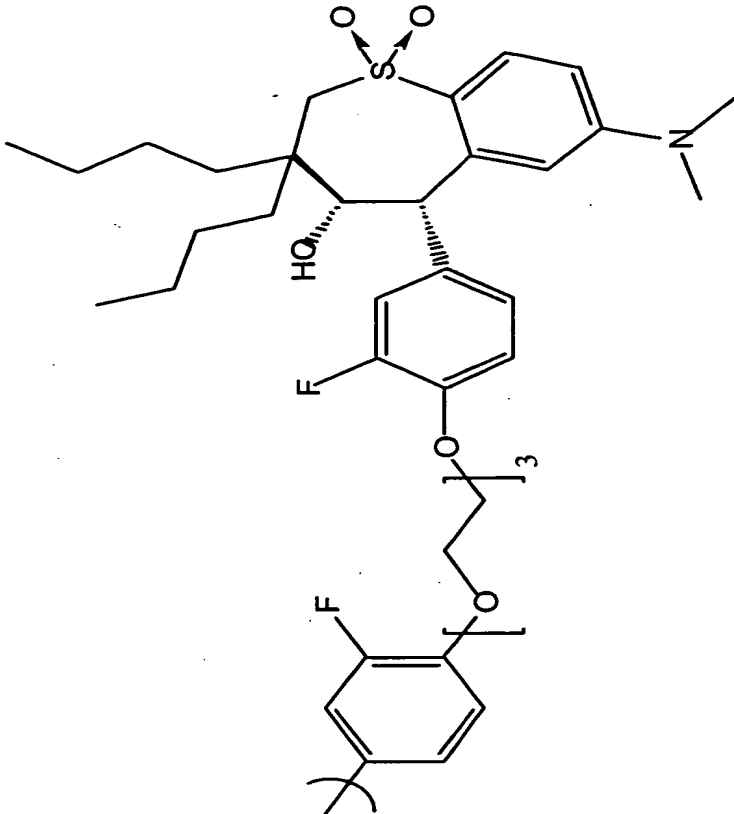
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1132	n-butyl	n-butyl	OH	H	
1133	n-butyl	n-butyl	OH	H	4-cyanomethylphenyl
1134	Ethyl	n-butyl	OH	H	
1135	n-butyl	n-butyl	OH	H	3,4-dimethoxyphenyl

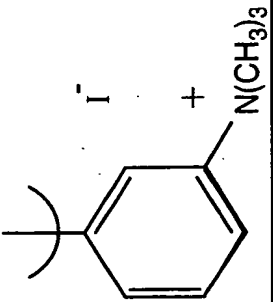
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1136	n-butyl	n-butyl	OH	H	
1137	n-butyl	n-butyl	OH	H	4-fluorophenyl
1138	n-butyl	n-butyl	OH	H	
1139	n-butyl	n-butyl	OH	H	3,4-difluorophenyl
1140	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1141	n-butyl	n-butyl	OH	H	4-fluorophenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1142	n-butyl	n-butyl	OH	H	
1143	n-butyl	n-butyl	H	OH	H
1144	n-butyl	n-butyl	OH	H	5-piperonyl
1145	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1146	n-butyl	n-butyl	OH	H	
1147	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1148	n-butyl	n-butyl	OH	H	4-fluorophenyl
1149	n-butyl	n-butyl	OH	H	4-fluorophenyl
1150	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1151	n-butyl	ethyl	OH	H	3-fluoro-4-methoxyphenyl
1152	n-butyl	n-butyl	OH	H	phenyl
1153	n-butyl	n-butyl	OH	H	4-fluorophenyl
1154	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1155	n-butyl	n-butyl	OH	H	4-fluorophenyl
1156	n-butyl	n-butyl	OH	H	4-fluorophenyl

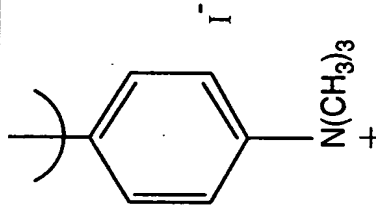
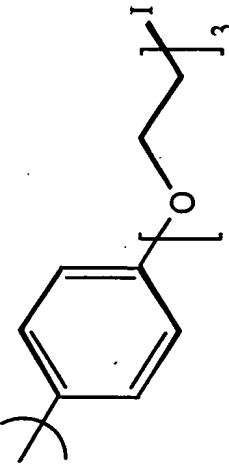
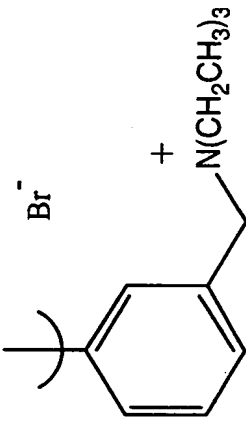
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1157	n-butyl	n-butyl	OH	H	4-fluorophenyl
1158	n-butyl	n-butyl	OH	H	4-pyridinyl, hydrochloride salt
1159	n-butyl	ethyl	OH	H	phenyl
1160	n-butyl	n-butyl	OH	H	4-fluorophenyl
1161	n-butyl	n-butyl	OH	H	3,5-dichloro-4-methoxyphenyl
1162	n-butyl	n-butyl	OH	H	phenyl
1163	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl
1164	n-butyl	n-butyl	OH	H	4-pyridinyl
1165	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1166	n-butyl	n-butyl	OH	H	3-hydroxyphenyl
1167	n-butyl	n-butyl	OH	H	
1168	n-butyl	n-butyl	OH	H	
1169	n-butyl	n-butyl	OH	H	
1170	n-butyl	n-butyl	OH	H	
1171	n-butyl	n-butyl	OH	H	
1172	n-butyl	n-butyl	OH	H	
1173	n-butyl	n-butyl	OH	H	
1174	Ethyl	n-butyl	OH	H	
1175	Ethyl	n-butyl	OH	H	
1176	n-butyl	n-butyl	OH	H	
1177	n-butyl	n-butyl	OH	H	

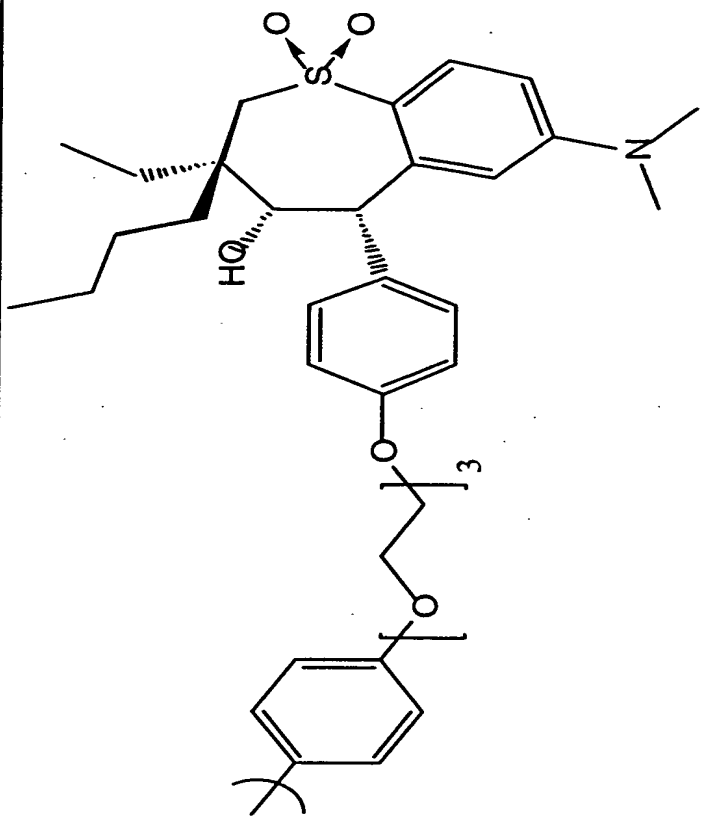
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1178	n-butyl	n-butyl	OH	H	3-(trifluoromethylsulfonyloxy)phenyl
1179	n-butyl	n-butyl	OH	H	phenyl
1180	n-butyl	n-butyl	OH	H	phenyl
1181	n-butyl	n-butyl	OH	H	4-fluorophenyl
1182	n-butyl	n-butyl	OH	H	4-(dimethylamino)phenyl
1183	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1184	n-butyl	n-butyl	OH	H	4-fluorophenyl
1185	n-butyl	n-butyl	OH	H	4-fluorophenyl
1186	n-butyl	n-butyl	OH	H	phenyl
1187	n-butyl	n-butyl	OH	H	4-fluorophenyl
1188	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1189	n-butyl	n-butyl	OH	H	3,4-difluorophenyl
1190	n-butyl	n-butyl	OH	H	2-bromophenyl
1191	n-butyl	n-butyl	OH	H	4-(dimethylamino)phenyl
1192	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl
1193	n-butyl	n-butyl	OH	H	4-(2-(2-methylpropyl))phenyl

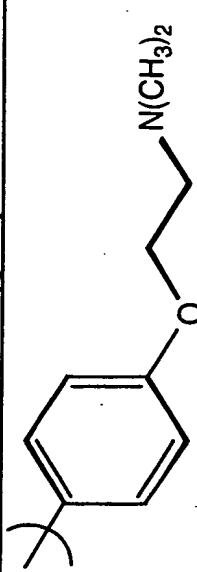
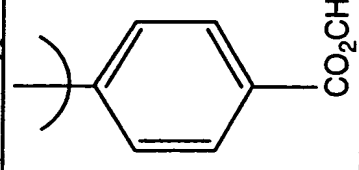
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1194	n-butyl	n-butyl	OH	H	
1195	n-butyl	n-butyl	OH	H	4-methoxyphenyl

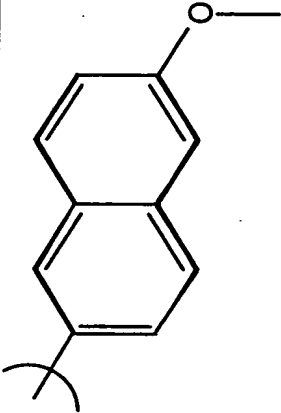
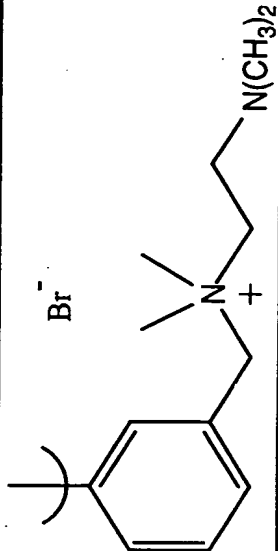
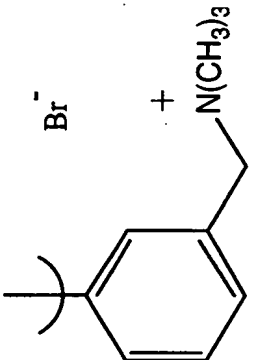
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1196	n-butyl	n-butyl	OH	H	
1197	n-butyl	ethyl	R3 + R4 = oxo	R3 + R4 = oxo	phenyl
1198	n-butyl	n-butyl	OH	H	4-(pyridinyl-N-oxide)

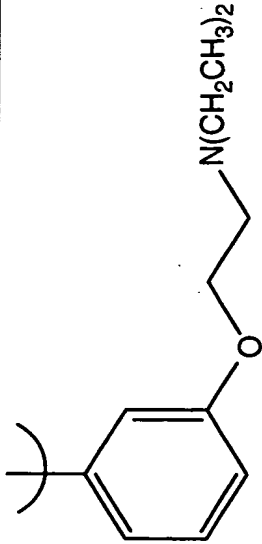
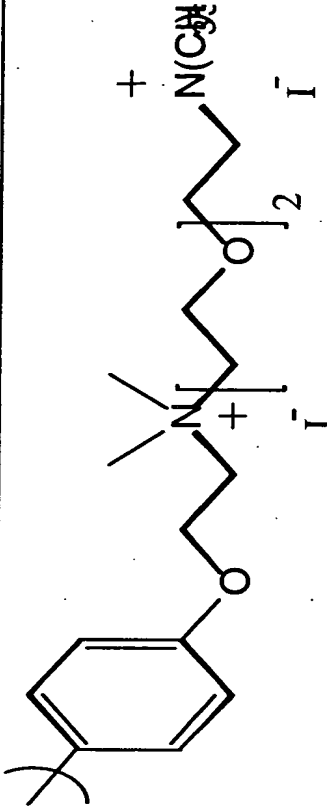
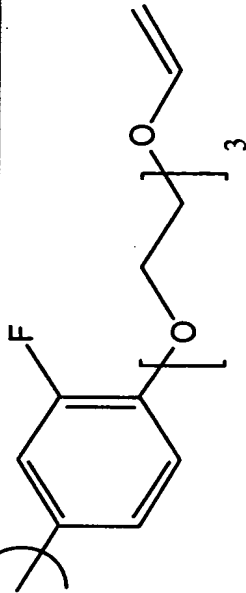
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1199	n-butyl	n-butyl	OH	H	
1200	n-butyl	n-butyl	H	OH	
1201	n-butyl	n-butyl	OH	H	

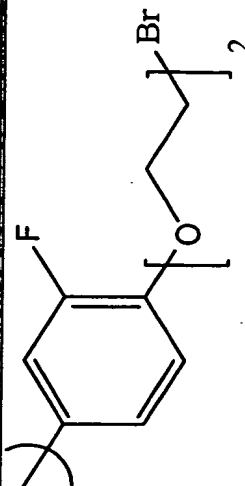
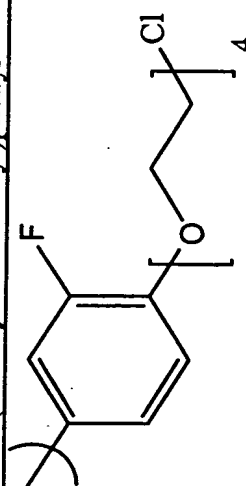
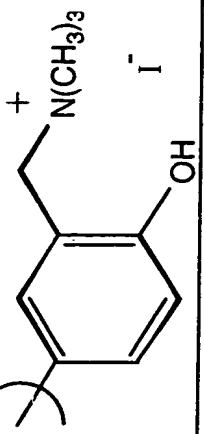
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1202	n-butyl	n-butyl	OH	H	
1203	n-butyl	n-butyl	OH	H	5-piperazinyl
1204	n-butyl	n-butyl	OH	H	4-fluorophenyl
1205	n-butyl	n-butyl	OH	H	
1206	n-butyl	n-butyl	OH	H	
1207	n-butyl	n-butyl	OH	H	3,5-dichlorophenyl

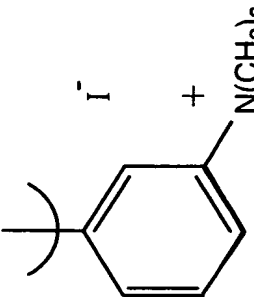
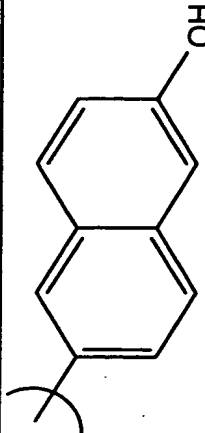
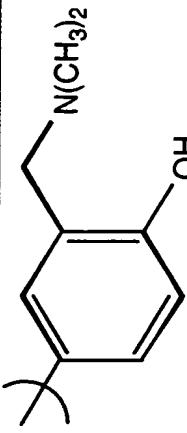
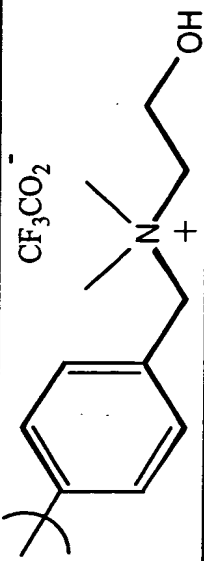
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1208	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1209	n-butyl	n-butyl	acetoxy	H	phenyl
1210	n-butyl	n-butyl	OH	H	2-(dimethylamino)phenyl
1211	Ethyl	n-butyl	OH	H	
1212	n-butyl	n-butyl	OH	H	
1213	n-butyl	ethyl	H	OH	
1214	n-butyl	ethyl	OH	H	
1215	n-butyl	n-butyl	OH	H	

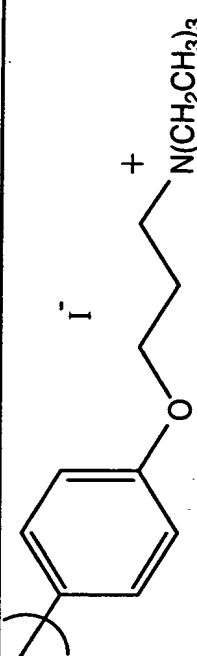
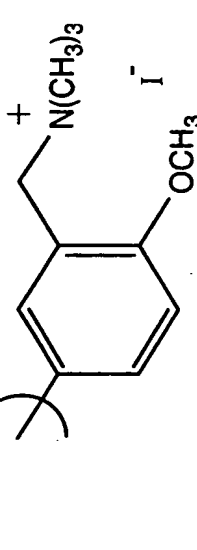
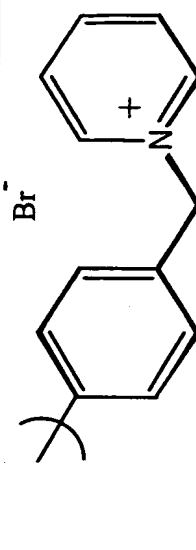
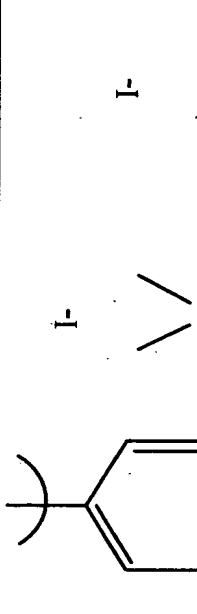
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1216	Ethyl	n-butyl	OH	H	5-piperonyl
1217	n-butyl	n-butyl	OH	H	4-carboxyphenyl
1218	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1219	n-butyl	n-butyl	OH	H	
1220	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1221	n-butyl	n-butyl	OH	H	
1222	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1223	n-butyl	n-butyl	OH	H	phenyl
1224	n-butyl	n-butyl	OH	H	3-nitrophenyl
1225	n-butyl	ethyl	OH	H	3-methylphenyl
1226	Ethyl	n-butyl	OH	H	5-piperonyl
1227	n-butyl	n-butyl	OH	H	4-fluorophenyl
1228	n-butyl	n-butyl	OH	H	2-pyrirolyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1229	n-butyl	n-butyl	OH	H	3-chloro-4-hydroxyphenyl
1230	n-butyl	n-butyl	OH	H	phenyl
1231	n-butyl	n-butyl	OH	H	
1232	n-butyl	n-butyl	H	OH	3-thiophenyl
1233	n-butyl	n-butyl	OH	H	
1234	n-butyl	n-butyl	OH	H	

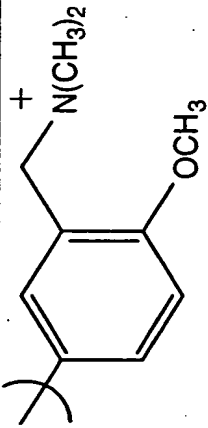
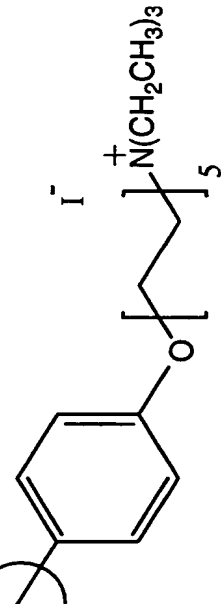
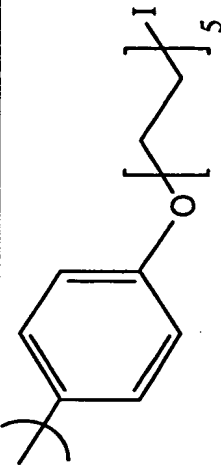
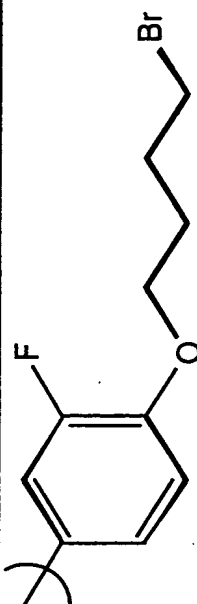
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1235	n-butyl	n-butyl	OH	H	
1236	n-butyl	n-butyl	OH	H	4-(bromomethyl)phenyl
1237	n-butyl	n-butyl	OH	H	
1238	n-butyl	n-butyl	OH	H	

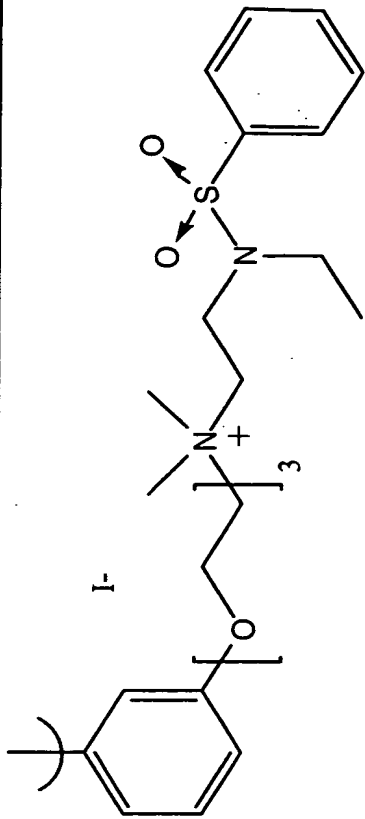
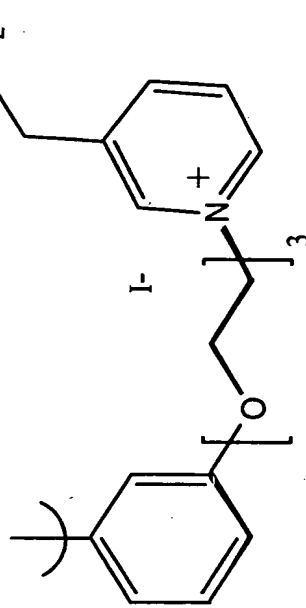
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1239	n-butyl	n-butyl	OH	H	
1240	n-butyl	n-butyl	OH	H	4-methoxy-3-methylphenyl
1241	n-butyl	n-butyl	OH	H	3-(dimethylaminomethyl)phenyl
1242	n-butyl	n-butyl	OH	H	
1243	n-butyl	n-butyl	OH	H	
1244	n-butyl	n-butyl	OH	H	3-methoxyphenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1245	n-butyl	n-butyl	OH	H	
1246	n-butyl	n-butyl	OH	H	3-(bromomethyl)phenyl
1247	n-butyl	n-butyl	OH	H	
1248	n-butyl	n-butyl	OH	H	
1249	n-butyl	n-butyl	OH	H	
1250	n-butyl	n-butyl	OH	H	3-(dimethylamino)phenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1251	n-butyl	n-butyl	OH	H	1-naphthyl
1252	n-butyl	n-butyl	OH	H	
1253	n-butyl	n-butyl	OH	H	
1254	n-butyl	n-butyl	OH	H	
1255	n-butyl	n-butyl	OH	H	
1256	n-butyl	n-butyl	OH	H	3-nitrophenyl

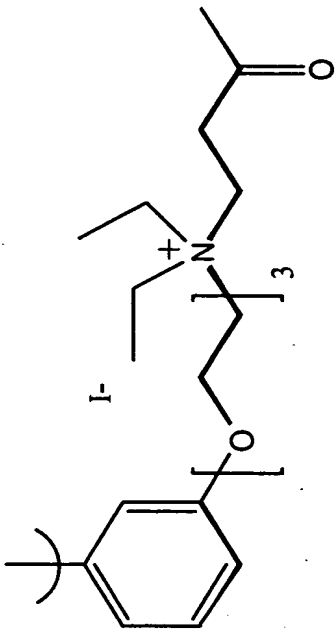
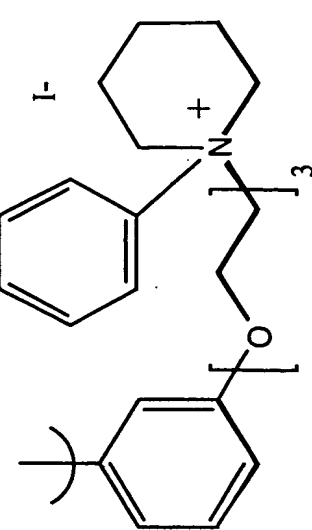
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1257	n-butyl	n-butyl	OH	H	phenyl
1258	n-butyl	n-butyl	OH	H	4-fluorophenyl
1259	Ethyl	n-butyl	H	OH	H
1260	Ethyl	n-butyl	OH	H	3-hydroxyphenyl
1261	n-butyl	n-butyl	OH	H	
1262	n-butyl	n-butyl	OH	H	
1263	n-butyl	n-butyl	OH	H	
1264	n-butyl	n-butyl	OH	H	
1265	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1266	n-butyl	n-butyl	OH	H	
1267	n-butyl	ethyl	OH	H	5-piperonyl
1268	n-butyl	n-butyl	OH	H	
1269	n-butyl	n-butyl	OH	H	
1270	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1271	n-butyl	n-butyl	OH	H	
1272	n-butyl	n-butyl	OH	H	

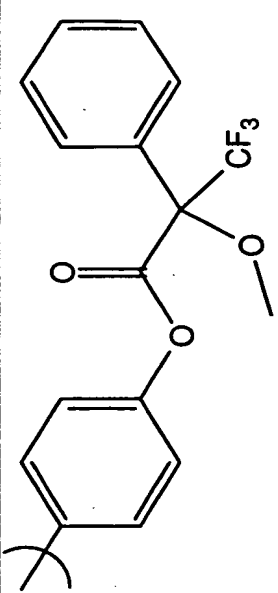
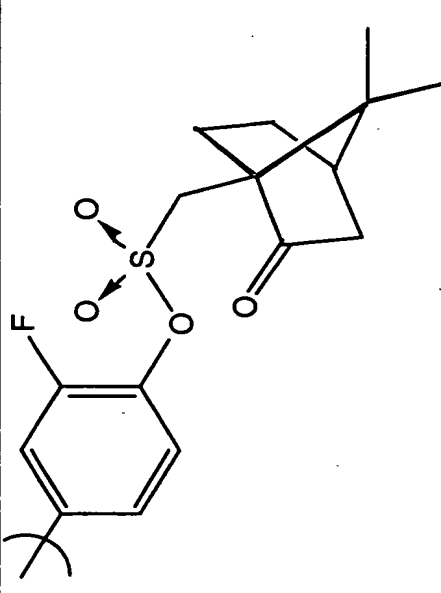
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1273	n-butyl	n-butyl	OH	H	
1274	n-butyl	n-butyl	OH	H	
1275	n-butyl	n-butyl	OH	H	

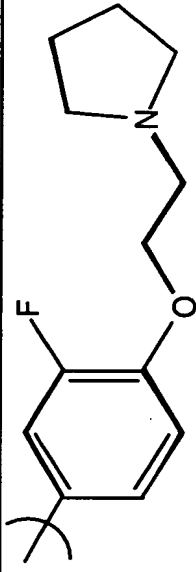
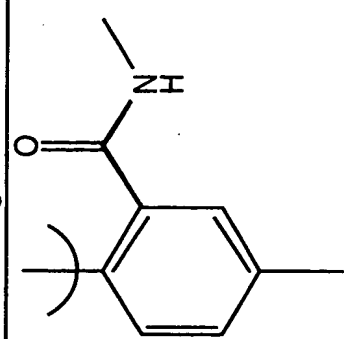
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1279	n-butyl	n-butyl	OH	H	
1280	n-butyl	n-butyl	OH	H	
1281	n-butyl	n-butyl	OH	H	
1282	Ethyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl
1283	n-butyl	n-butyl	OH	H	4-hydroxymethylphenyl
1284	n-butyl	n-butyl	OH	H	4-fluorophenyl
1285	n-butyl	ethyl	OH	H	phenyl

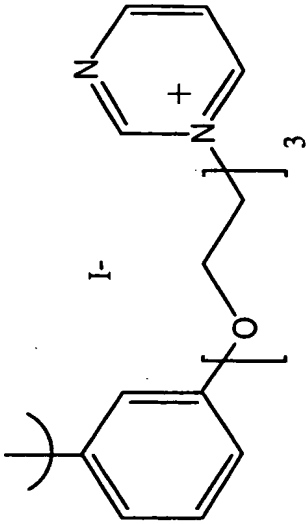
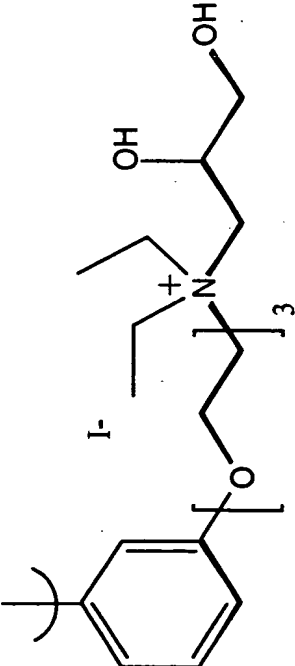
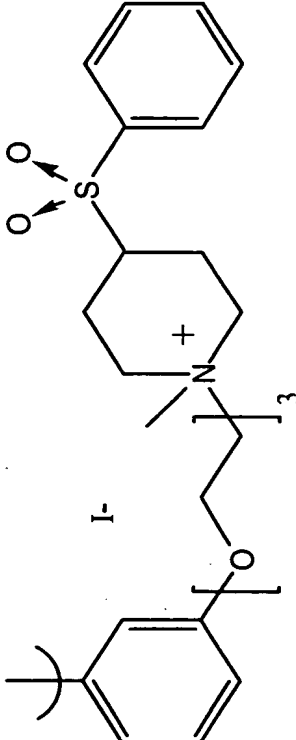
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1293	n-butyl	n-butyl	OH	H	
1294	n-butyl	n-butyl	OH	H	

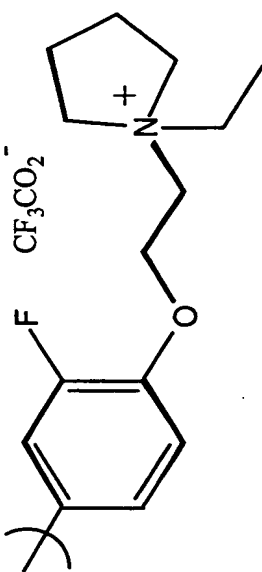
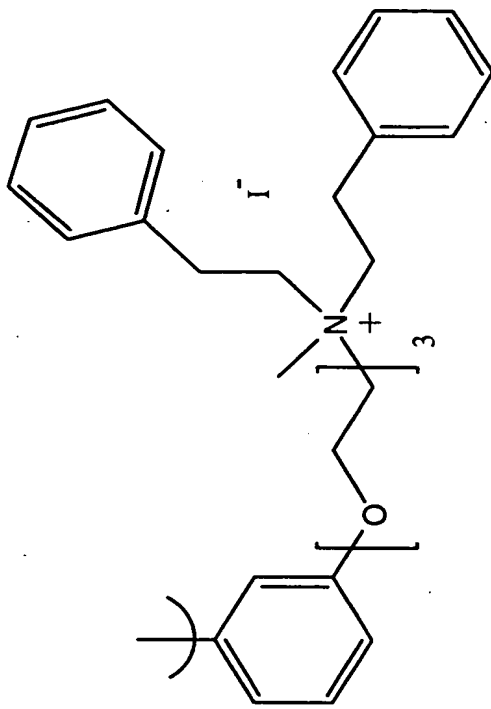
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1295	n-butyl	n-butyl	OH	H	
1296	n-butyl	n-butyl	OH	H	
1297	n-butyl	n-butyl	OH	H	

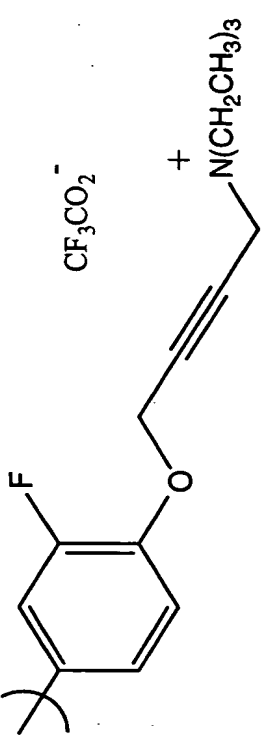
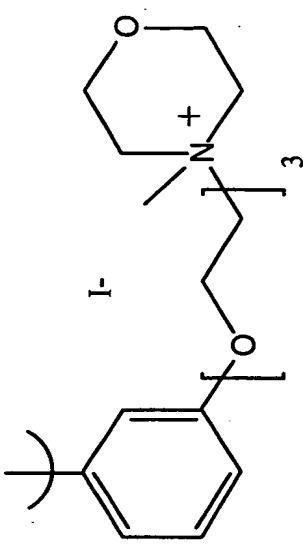
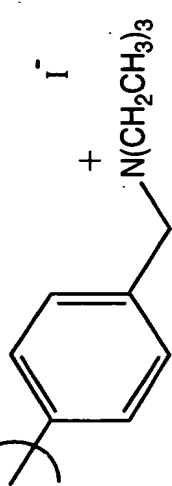
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1298	n-butyl	n-butyl	OH	H	
1299	n-butyl	n-butyl	OH	H	
1300	n-butyl	ethyl	H	OH	H
1301	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1302	n-butyl	n-butyl	OH	H	3-hydroxyphenyl
1303	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1304	n-butyl	n-butyl	OH	H	3-methoxyphenyl
1305	n-butyl	n-butyl	OH	H	4-fluorophenyl
1306	n-butyl	n-butyl	OH	H	
1307	n-butyl	n-butyl	OH	H	H
1308	Ethyl	n-butyl	OH	H	
1309	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1310	Ethyl	n-butyl	OH	H	phenyl
1311	n-butyl	ethyl	OH	H	phenyl

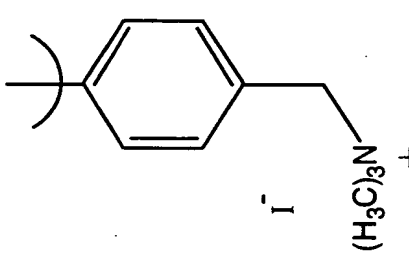
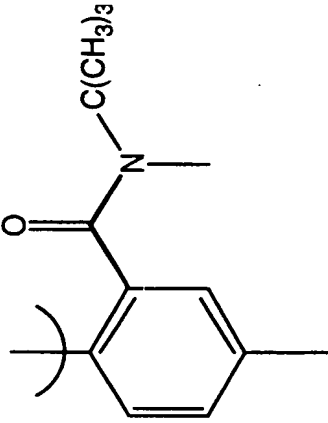
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1312	n-butyl	ethyl	OH	H	phenyl
1313	n-butyl	ethyl	OH	H	phenyl
1314	Ethyl	n-butyl	OH	H	phenyl
1315	Ethyl	n-butyl	OH	H	phenyl
1316	n-butyl	ethyl	OH	H	phenyl
1317	n-butyl	ethyl	OH	H	phenyl
1318	Ethyl	n-butyl	OH	H	phenyl
1319	Ethyl	n-butyl	OH	H	3-methoxyphenyl
1320	Ethyl	n-butyl	OH	H	phenyl
1321	n-butyl	ethyl	OH	H	phenyl
1322	n-butyl	n-butyl	OH	H	
1323	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1324	n-butyl	n-butyl	OH	H	
1325	n-butyl	n-butyl	OH	H	4-((diethylamino)methyl)phenyl
1326	n-butyl	n-butyl	OH	H	
1327	n-butyl	n-butyl	OH	H	3-fluoro-4-hydroxy-5-iodophenyl
1328	n-butyl	n-butyl	OH	H	

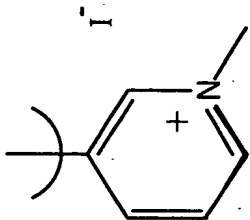
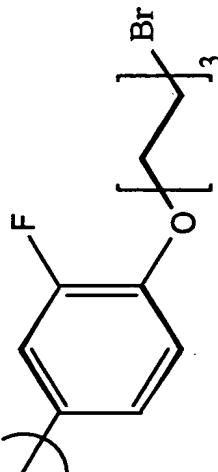
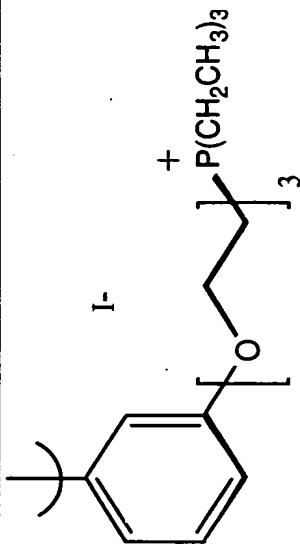
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1329	n-butyl	n-butyl	OH	H	
1330	n-butyl	n-butyl	OH	H	

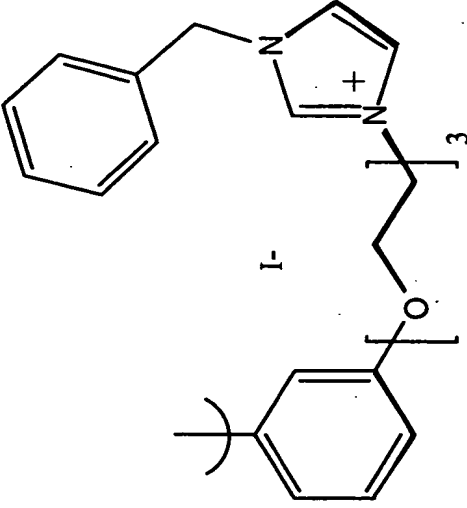
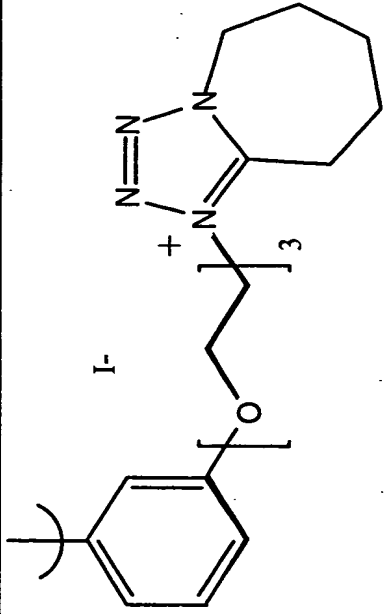
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1331	n-butyl	n-butyl	OH	H	
1332	n-butyl	n-butyl	OH	H	
1333	n-butyl	n-butyl	OH	H	

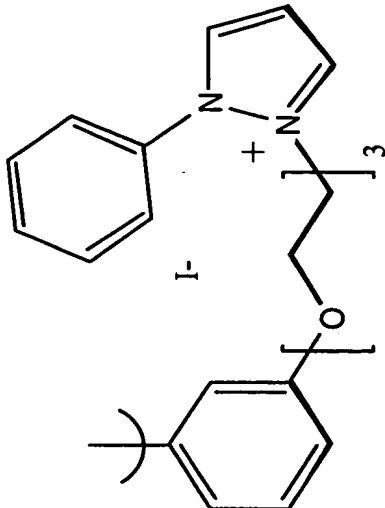
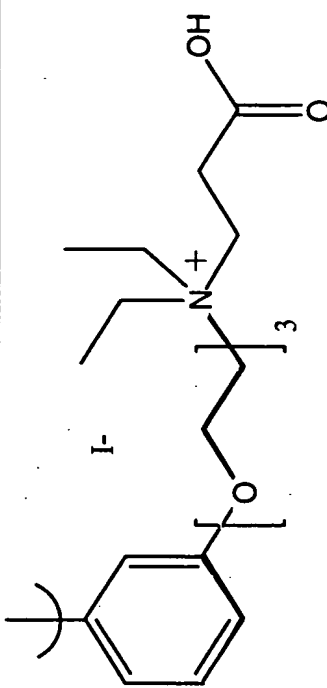
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1334	n-butyl	n-butyl	OH	H	
1335	n-butyl	n-butyl	OH	H	
1336	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1337	n-butyl	n-butyl	OH	H	 I^- $(\text{H}_3\text{C})_3\text{N}^+$
1338	n-butyl	n-butyl	OH	H	4-methoxyphenyl
1339	n-butyl	n-butyl	OH	H	
1340	n-butyl	ethyl	OH	H	5-piperonyl
1341	n-butyl	n-butyl	acetoxy	H	3-methoxyphenyl
1342	n-butyl	n-butyl	OH	H	5-piperonyl
1343	Ethyl	n-butyl	OH	H	phenyl
1344	n-butyl	n-butyl	OH	H	3-fluoro-4-methoxyphenyl

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1353	n-butyl	n-butyl	OH	H	
1354	n-butyl	n-butyl	OH	H	
1355	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1356	n-butyl	n-butyl	OH	H	
1357	n-butyl	n-butyl	OH	H	
1358	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1359	n-butyl	n-butyl	OH	H	
1360	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1361	n-butyl	n-butyl	OH	H	
1362	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1363	n-butyl	n-butyl	OH	H	
1364	n-butyl	n-butyl	OH	H	
1365	n-butyl	n-butyl	OH	H	

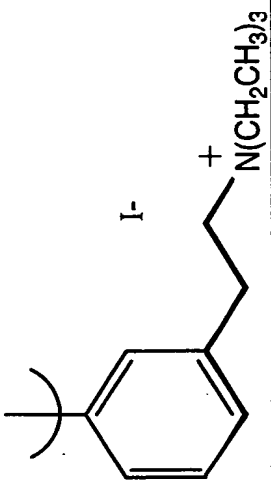
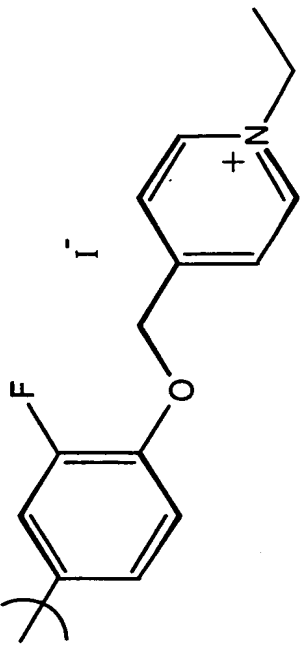
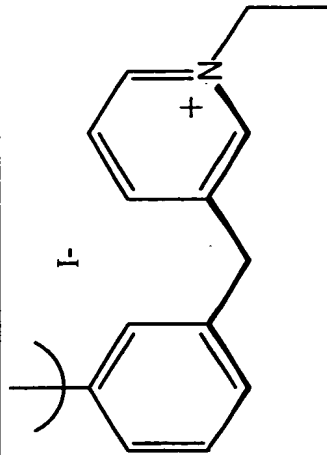
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1366	n-butyl	n-butyl	OH	H	
1367	n-butyl	n-butyl	OH	H	
1368	n-butyl	n-butyl	OH	H	

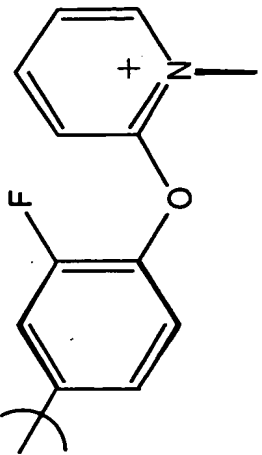
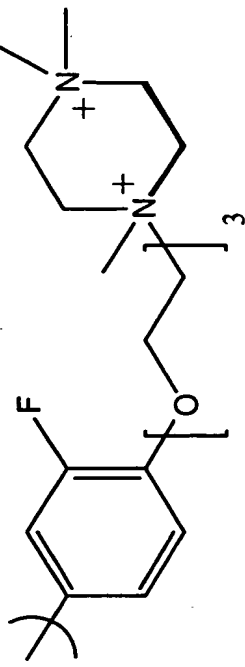
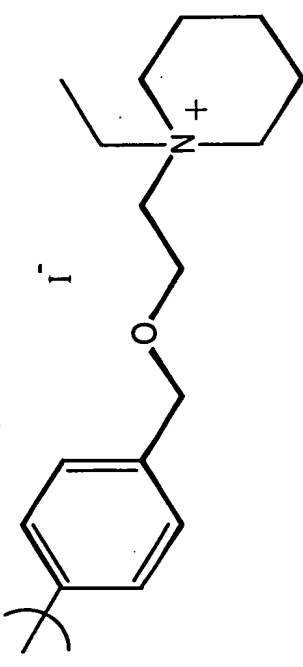
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1369	n-butyl	n-butyl	OH	H	
1370	n-butyl	n-butyl	OH	H	

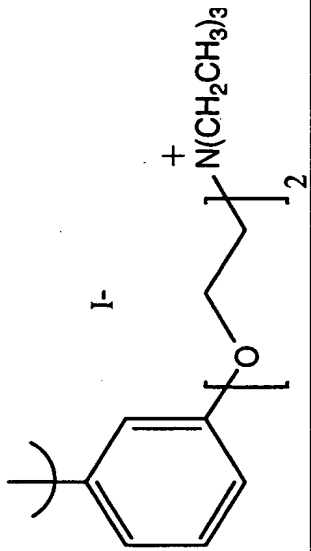
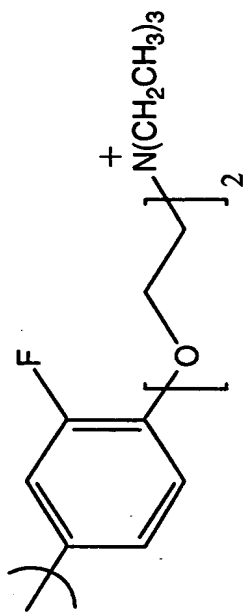
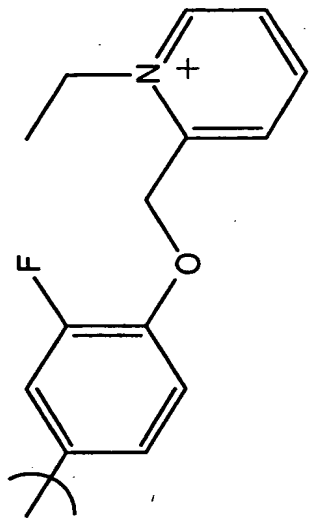
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1371	n-butyl	n-butyl	OH	H	
1372	n-butyl	n-butyl	OH	H	
1373	n-butyl	n-butyl	OH	H	

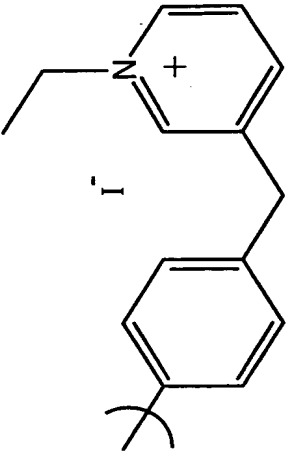
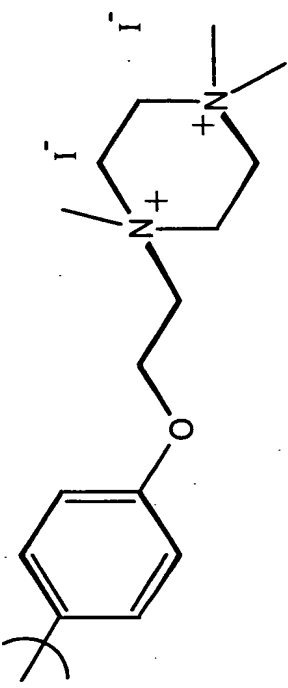
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1374	n-butyl	n-butyl	OH	H	
1375	n-butyl	n-butyl	OH	H	
1376	n-butyl	n-butyl	OH	H	

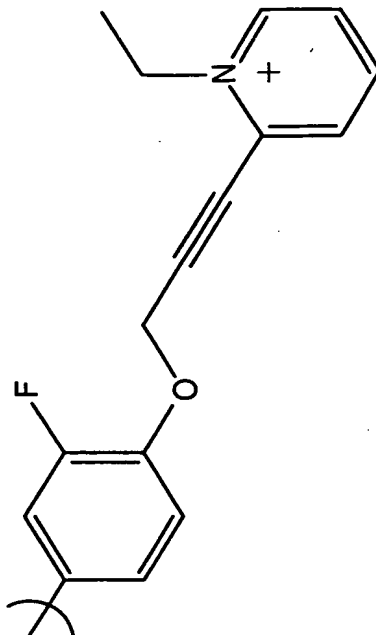
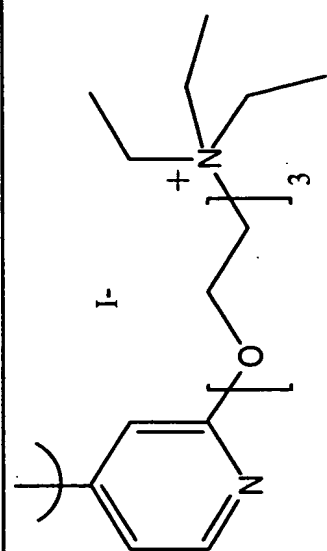
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1377	n-butyl	n-butyl	OH	H	
1378	n-butyl	n-butyl	OH	H	
1379	n-butyl	n-butyl	OH	H	

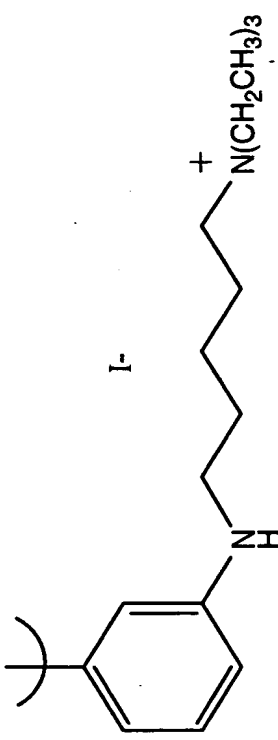
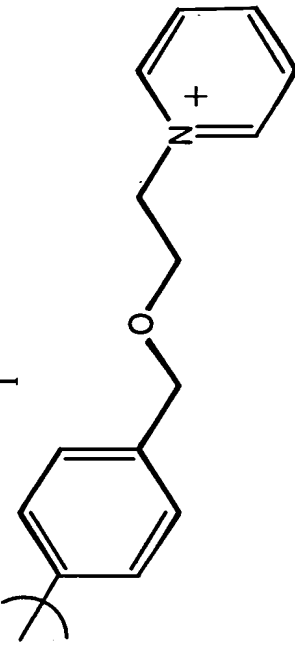
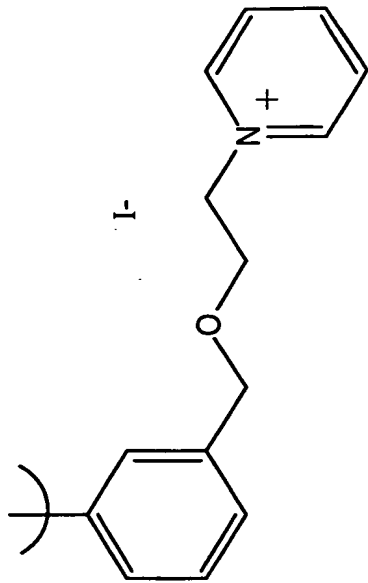
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1380	n-butyl	n-butyl	OH	H	
1381	n-butyl	n-butyl	OH	H	
1382	n-butyl	n-butyl	OH	H	

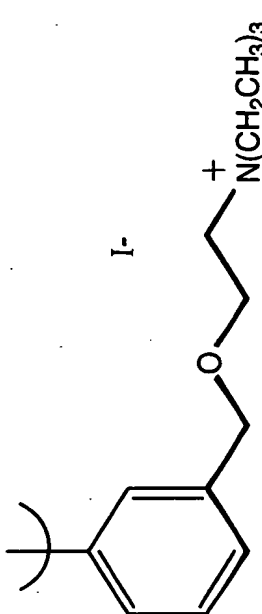
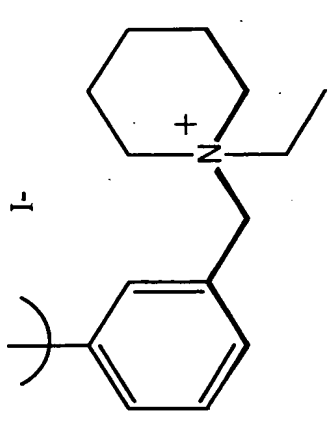
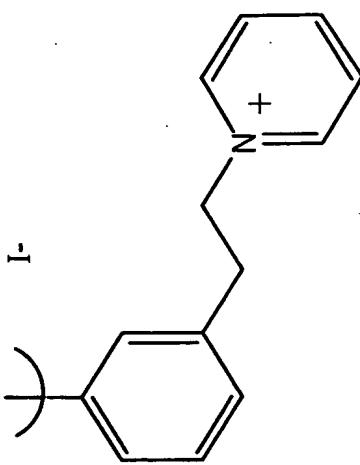
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1383	n-butyl	n-butyl	OH	H	
1384	n-butyl	n-butyl	OH	H	
1385	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1386	n-butyl	n-butyl	OH	H	
1387	n-butyl	n-butyl	OH	H	
1388	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1389	n-butyl	n-butyl	OH	H	
1390	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1391	n-butyl	n-butyl	OH	H	
1392	n-butyl	n-butyl	OH	H	

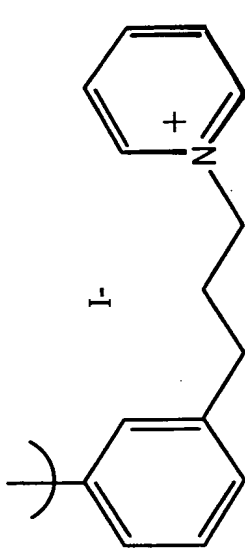
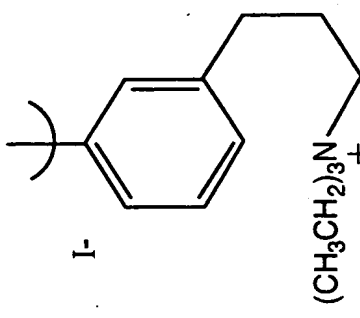
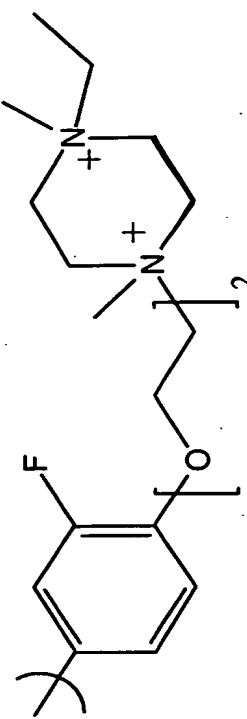
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1393	n-butyl	n-butyl	OH	H	
1394	n-butyl	n-butyl	OH	H	
1395	n-butyl	n-butyl	OH	H	

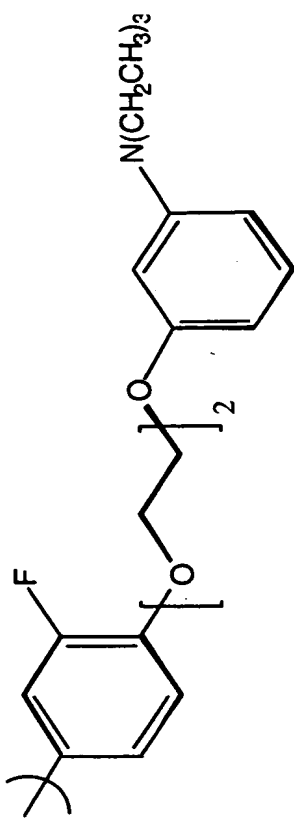
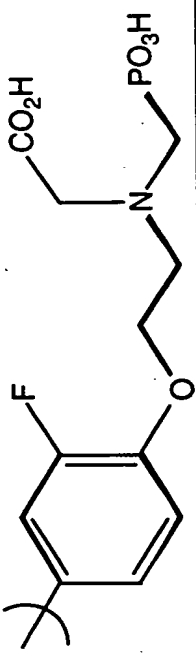
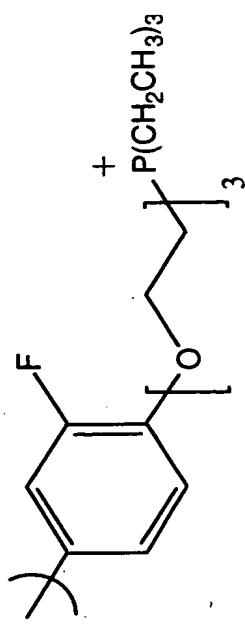
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1396	n-butyl	n-butyl	OH	H	
1397	n-butyl	n-butyl	OH	H	
1398	n-butyl	n-butyl	OH	H	

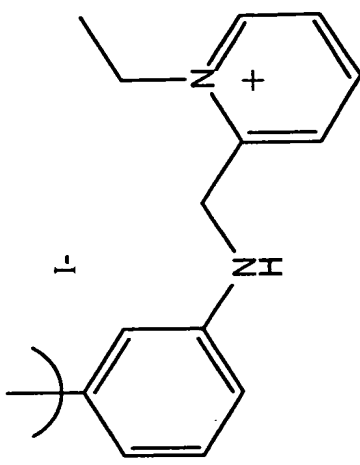
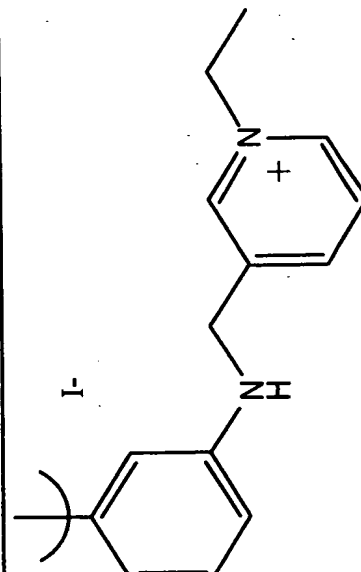
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1399	n-butyl	n-butyl	OH	H	
1400	n-butyl	n-butyl	OH	H	

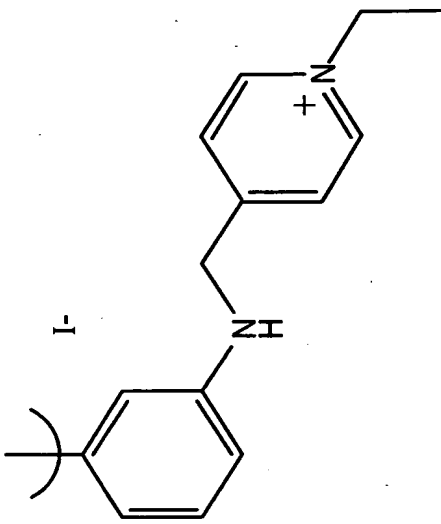
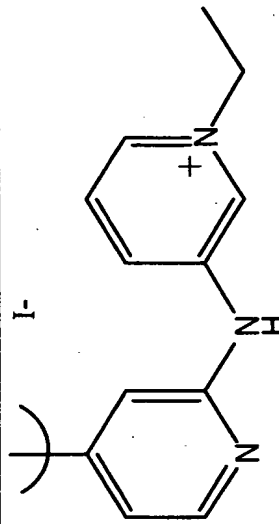
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1401	n-butyl	n-butyl	OH	H	
1402	n-butyl	n-butyl	OH	H	

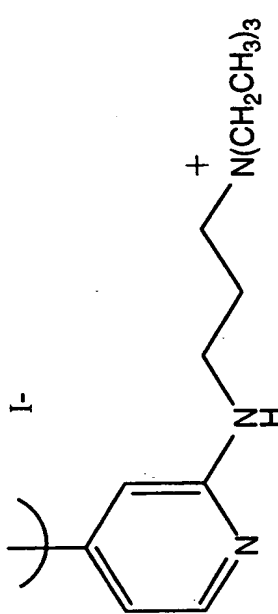
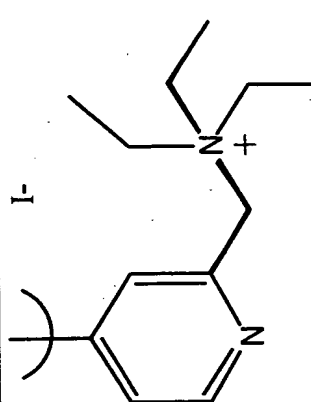
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1403	n-butyl	n-butyl	OH	H	
1404	n-butyl	n-butyl	OH	H	
1405	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1406	n-butyl	n-butyl	OH	H	
1407	n-butyl	n-butyl	OH	H	
1408	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1409	n-butyl	n-butyl	OH	H	
1410	n-butyl	n-butyl	OH	H	
1411	n-butyl	n-butyl	OH	H	

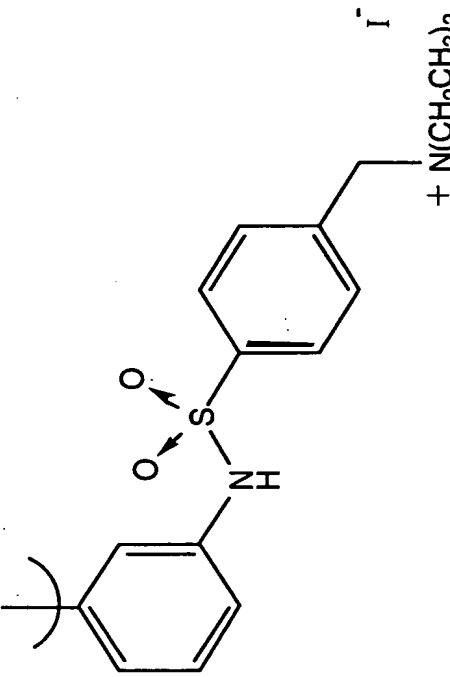
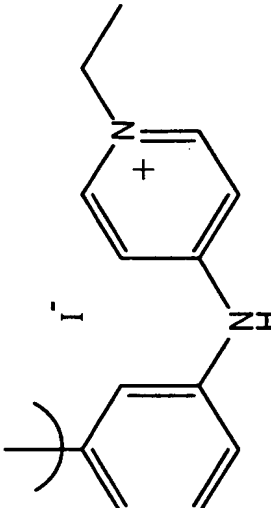
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1412	n-butyl	n-butyl	OH	H	
1413	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1414	n-butyl	n-butyl	OH	H	
1415	n-butyl	n-butyl	OH	H	

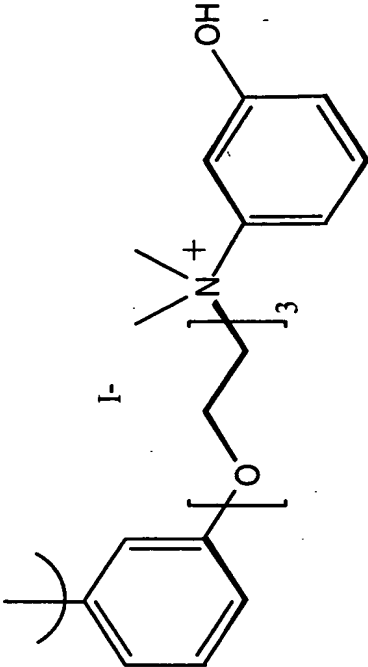
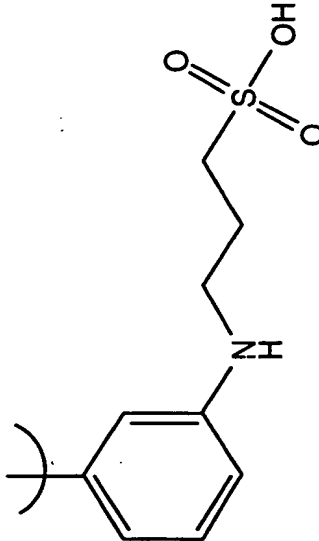
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1416	n-butyl	n-butyl	OH	H	
1417	n-butyl	n-butyl	OH	H	

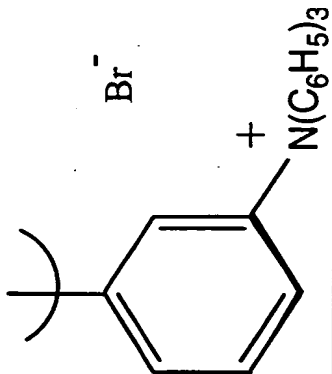
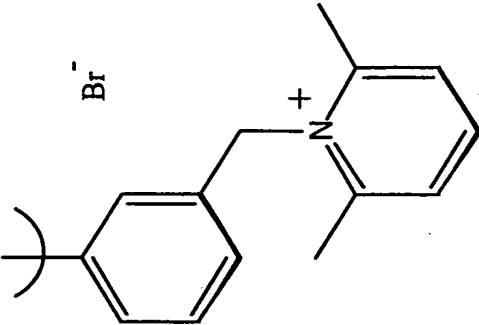
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1418	n-butyl	n-butyl	OH	H	
1419	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1420	n-butyl	n-butyl	OH	H	
1421	n-butyl	n-butyl	OH	H	

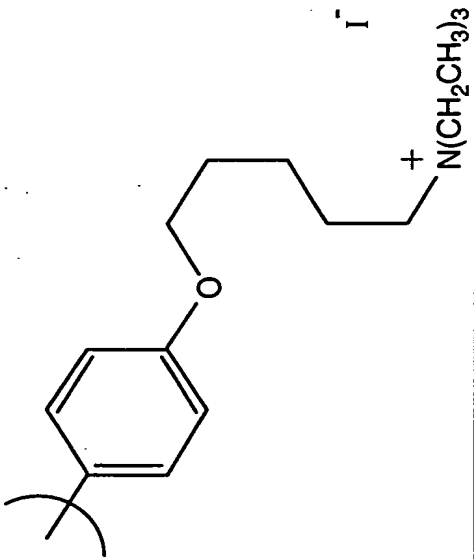
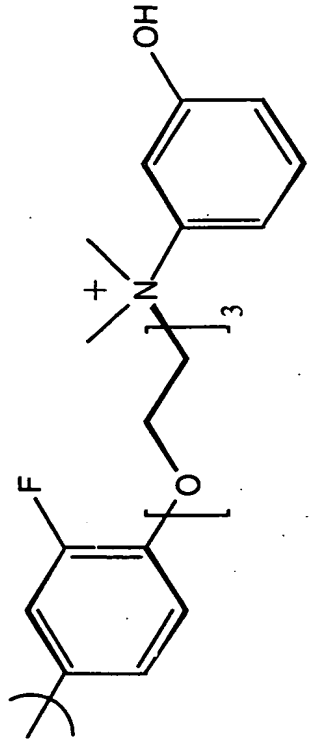
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1422	n-butyl	n-butyl	OH	H	 + N(CH ₂ CH ₂ CH ₃) ₃ I ⁻
1423	n-butyl	n-butyl	OH	H	 I ⁻

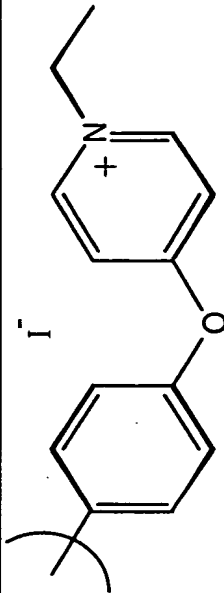
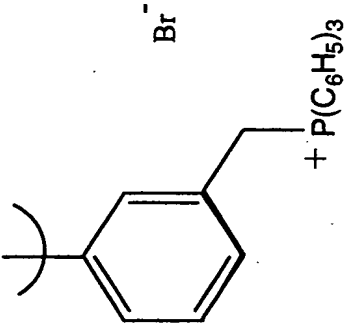
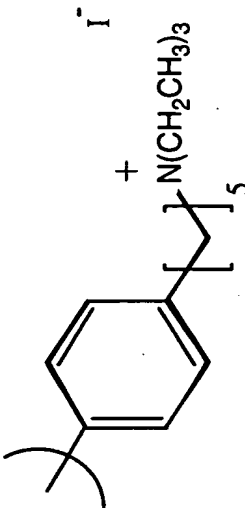
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1424	n-butyl	n-butyl	OH	H	
1425	n-butyl	n-butyl	OH	H	
1426	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1427	n-butyl	n-butyl	OH	H	
1428	n-butyl	n-butyl	OH	H	

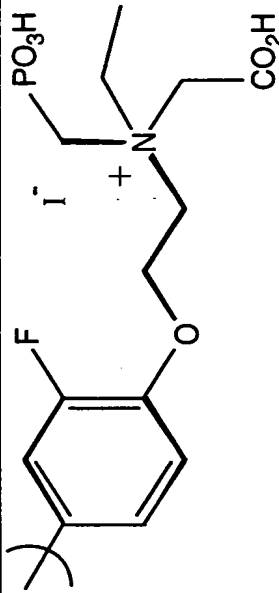
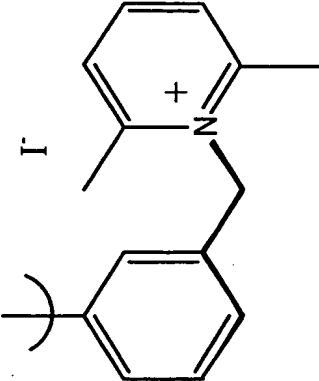
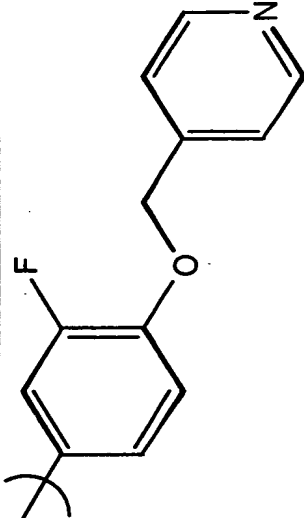
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1429	n-butyl	n-butyl	OH	H	
1430	n-butyl	n-butyl	OH	H	

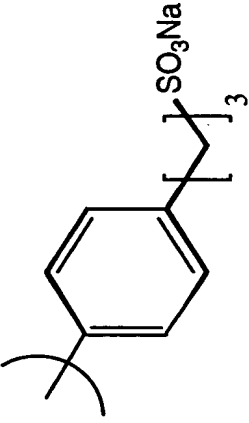
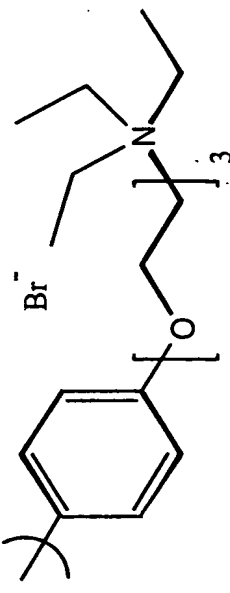
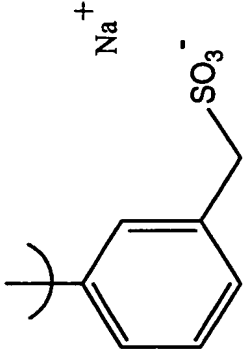
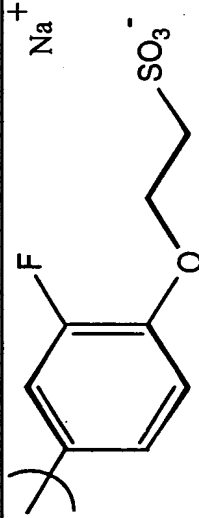
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1431	n-butyl	n-butyl	OH	H	
1432	n-butyl	n-butyl	OH	H	
1433	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1434	n-butyl	n-butyl	OH	H	
1435	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1436	n-butyl	n-butyl	OH	H	
1437	n-butyl	n-butyl	OH	H	
1438	n-butyl	n-butyl	OH	H	

Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1439	n-butyl	n-butyl	OH	H	
1440	n-butyl	n-butyl	OH	H	
1441	n-butyl	n-butyl	OH	H	

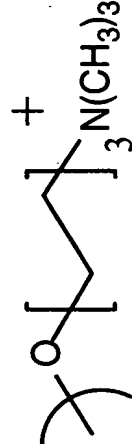
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1442	n-butyl	n-butyl	OH	H	
1443	n-butyl	n-butyl	OH	H	
1444	n-butyl	n-butyl	OH	H	

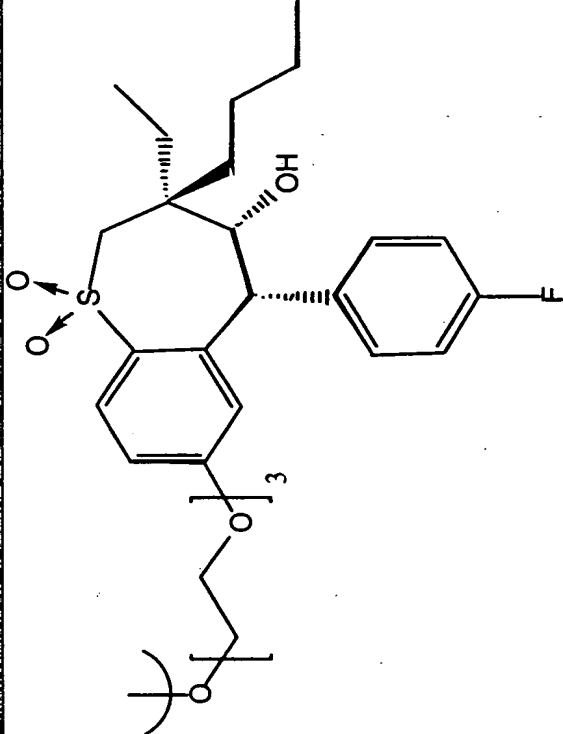
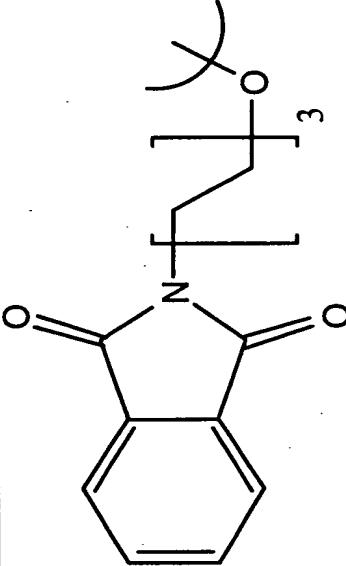
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1445	n-butyl	n-butyl	OH	H	
1446	n-butyl	n-butyl	OH	H	
1447	n-butyl	n-butyl	OH	H	
1448	n-butyl	n-butyl	OH	H	

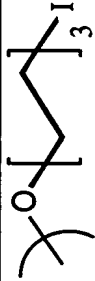
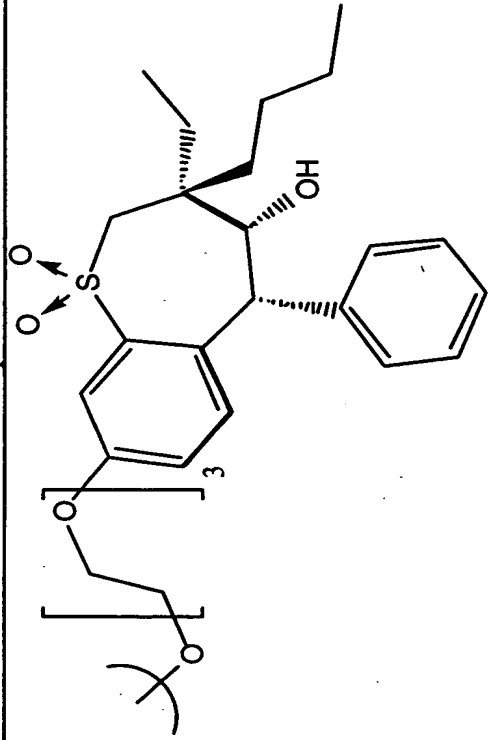
Compound Number	R ^{3A}	R ^{3B}	R ^{4A}	R ^{4B}	R ^{5A}
1449	n-butyl	n-butyl	OH	H	
1450	n-butyl	n-butyl	OH	H	phenyl
1451	n-butyl	n-butyl	OH	H	

Table 7

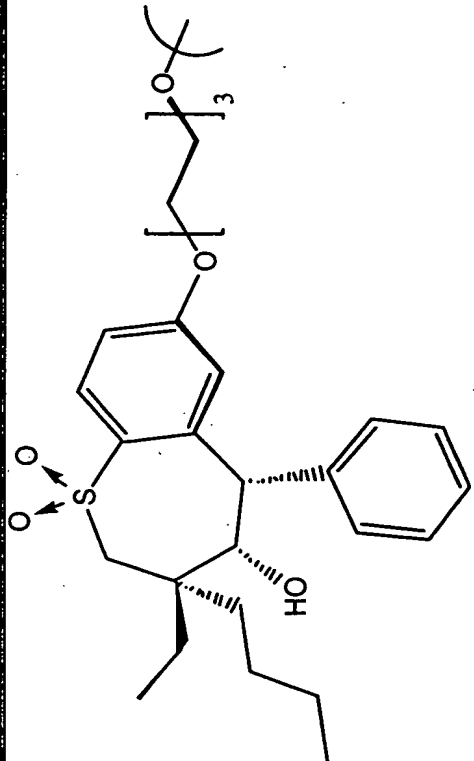
Compound Number	R ^{5B}	(R ⁶) _m
101	H	
102	H	7-trimethylammonium iodide
103	H	7-trimethylammonium iodide
104	H	7-dimethylamino
105	H	7-methanesulfonamido
106	H	7-(2'-bromoacetamido)
107	H	7-amino
108	H	7-(hexylamido)
109	H	7-amino
110	H	7-acetamido

Compound Number	R ^{5B}	(R ⁶) _m
111	H	7-amino
112	H	7-amino
113	H	7-amino
114	H	7-amino
115	H	7-(O-benzylcarbamato)
116	H	7-(O-benzylcarbamato)
117	H	7-(O-benzylcarbamato)
118	H	7-(O-benzylcarbamato)
119	H	7-(O-tert-butylcarbamato)
120	H	7-(O-benzylcarbamato)
121	H	7-amino
122	H	7-amino
123	H	7-hexylamino
124	H	7-(hexylamino)
125	H	I ⁻
		 at the 8-position
126	H	7-(O-benzylcarbamato)
127	H	7-amino
128	H	7-(O-benzylcarbamato)
129	H	7-amino

Compound Number	R^{5B}	$(R^6)_m$
131	H	 <p>at the 7-position</p>
132	H	 <p>at the 8-position</p>

Compound Number	R ^{5B}	(R ⁶) _m
133	H	8-(hexyloxy)
134	H	
135	H	 at the 8-position
136	H	8-hydroxy

Compound Number	R ^{5B}	(R ⁶) _m
137	H	
138	H	<p>at the 7-position 8-acetoxy</p>

Compound Number	R ^{5B}	(R ⁶) _m
139	H	
140		at the 7-position
141		
142	3-methoxy-phenyl	7-methylmercapto
143	H	7-methylmercapto
144	H	7-(N-azetidiny)
262	H	7-methoxy
263	3-methoxy-phenyl	7-methoxy
264	H	7-methoxy
265	3-trifluoro-methyl-phenyl	7-methoxy
266	H	7-hydroxy

Compound Number	R ^{5B}	(R ⁶) _m
267	H	7-methoxy
268	H	7-methoxy
269	4-fluoro-phenyl	7-methoxy
270	H	7-hydroxy
271	H	7-bromo
272	3-methoxy-phenyl	7-bromo
273	4-fluoro-phenyl	7-fluoro
274	H	7-fluoro
275	3-methoxy-phenyl	7-fluoro
276	H	7-fluoro
277	H	7-methoxy
278	H	7-methoxy
279	H	7-methoxy
280	H	7-methoxy
281	H	7-methylmercapto
282	H	7-methyl
283	4-fluoro-phenyl	7-methyl
284	H	7-(4'-morpholino)
286	H	7-(O-benzylcarbamato)
287	H	7-amino
288	H	7-amino
289	H	7-amino
290	H	7-amino
291	H	7-(O-benzylcarbamato)

Compound Number	R ^{SB}	(R ⁶) _m
292	H	7-amino
293	H	7-benzylamino
294	H	7-dimethylamino
295	H	7-amino
296	H	7-amino
1000	H	7-dimethylamino
1001	H	7-dimethylamino
1002	H	7-dimethylamino
1003	H	7-dimethylamino
1004	H	7-dimethylamino
1005	H	7-dimethylamino
1006	H	7-dimethylamino
1007	H	7-dimethylamino
1008	H	7-dimethylamino
1009	H	7-dimethylamino
1010	H	7-dimethylamino
1011	H	7-dimethylamino
1012	H	7-dimethylamino; 9-methoxy
1013	H	7-dimethylamino
1014	H	7-dimethylamino; 9-methoxy
1015	H	7-dimethylamino
1016	H	7-dimethylamino
1017	H	7-dimethylamino
1018	H	7-dimethylamino
1019	H	7-dimethylamino
1020	H	7-dimethylamino

Compound Number	R ^{5B}	(R ⁶) _m
1021	H	7-dimethylamino
1022	H	7-dimethylamino
1023	H	7-dimethylamino
1024	H	7-dimethylamino
1025	H	7-dimethylamino
1026	H	7-dimethylamino
1027	H	7-dimethylamino
1028	H	7-dimethylamino
1029	H	7-dimethylamino
1030	H	7-dimethylamino
1031	H	7-dimethylamino
1032	H	7-dimethylamino
1033	H	7-dimethylamino
1034	H	7-dimethylamino
1035	H	7-dimethylamino
1036	H	7-dimethylamino
1037	H	7-dimethylamino
1038	H	7-dimethylamino
1039	H	7-dimethylamino
1040	H	7-dimethylamino
1041	H	7-dimethylamino
1042	H	7-dimethylamino
1043	H	7-dimethylamino
1044	H	7-dimethylamino
1045	H	7-dimethylamino
1046	H	7-dimethylamino

Compound Number	R ^{SB}	(R ⁶) _m
1047	H	7-dimethylamino
1048	H	7-dimethylamino
1049	H	7-dimethylamino
1050	H	7-dimethylamino
1051	H	7-dimethylamino
1052	H	7-dimethylamino
1053	H	7-dimethylamino
1054	H	7-dimethylamino
1055	H	7-dimethylamino
1056	H	7-dimethylamino
1057	H	7-dimethylamino
1058	H	7-dimethylamino
1059	H	7-dimethylamino
1060	H	7-methylamino
1061	H	7-methylamino
1062	H	7-methylamino
1063	H	7-methylamino
1064	H	7-methylamino
1065	H	7-dimethylamino
1066	H	7-dimethylamino
1067	H	9-dimethylamino
1068	H	7-dimethylamino
1069	H	7-dimethylamino; 9-dimethylamino
1070	H	7-dimethylamino
1071	H	7-dimethylamino

Compound Number	R ^{5B}	(R ⁶) _m
1072	H	7-dimethylamino
1073	H	7-dimethylamino
1074	H	7-dimethylamino
1075	H	7-dimethylamino; 9-dimethylamino
1076	H	7-dimethylamino
1077	H	7-dimethylamino
1078	H	7-dimethylamino
1079	H	7-dimethylamino
1080	H	7-dimethylamino
1081	H	7-dimethylamino
1082	H	7-dimethylamino
1083	H	7-dimethylamino
1084	H	7-dimethylamino
1085	H	7-dimethylamino
1086	H	7-dimethylamino
1087	H	7-dimethylamino
1088	H	7-dimethylamino
1089	H	7-dimethylamino
1090	H	7-dimethylamino
1091	H	7-dimethylamino
1092	H	7-dimethylamino
1093	H	7-dimethylamino
1094	H	7-dimethylamino
1095	H	7-dimethylamino
1096	H	7-dimethylamino
1097	H	7-dimethylamino

Compound Number	R ^{5B}	(R ⁶) _m
1098	H	7-dimethylamino
1099	H	7-dimethylamino
1100	H	7-dimethylamino
1101	H	7-dimethylamino
1102	H	7-dimethylamino
1103	H	7-dimethylamino
1104	H	7-dimethylamino
1105	H	7-dimethylamino
1106	H	7-dimethylamino
1107	H	7-dimethylamino
1108	H	7-dimethylamino
1109	H	7-dimethylamino
1110	H	7-dimethylamino
1111	H	7-dimethylamino
1112	H	7-dimethylamino
1113	H	7-dimethylamino
1114	H	7-methylamino
1115	H	7-dimethylamino
1116	H	7-dimethylamino
1117	H	7-dimethylamino
1118	H	7-dimethylamino
1119	H	7-dimethylamino
1120	H	7-dimethylamino
1121	H	7-dimethylamino
1122	H	7-dimethylamino
1123	H	7-dimethylamino

Compound Number	R ^{SB}	(R ⁶) _m
1124	H	7-dimethylamino
1125	H	7-dimethylamino
1126	H	7-dimethylamino
1127	H	7-dimethylamino
1128	H	7-dimethylamino
1129	H	9-dimethylamino
1130	H	7-dimethylamino
1131	H	7-dimethylamino
1132	H	7-dimethylamino
1133	H	7-dimethylamino
1134	H	7-dimethylamino
1135	H	7-dimethylamino
1136	H	7-dimethylamino
1137	H	9-(2',2'-dimethylhydrazino)
1138	H	7-dimethylamino
1139	H	7-dimethylamino
1140	H	7-(2',2'-dimethylhydrazino)
1141	H	7-ethylmethylamino
1142	H	7-dimethylamino
1143	3-fluoro-4-methoxy-phenyl	7-dimethylamino
1144	H	7-dimethylamino
1145	H	9-dimethylamino
1146	H	7-dimethylamino
1147	H	7-diethylamino

Compound Number	R ^{SB}	(R') _m
1148	H	7-dimethylsulfonium, fluoride salt
1149	H	7-ethylamino
1150	H	7-ethylmethylamino
1151	H	7-dimethylamino
1152	H	7-(ethoxymethyl) methylamino
1153	H	7-methylamino
1154	H	9-methoxy
1155	H	7-methyl
1156	H	7-methylmercapto
1157	H	7-fluoro; 9-dimethylamino
1158	H	7-methoxy
1159	H	7-dimethylamino
1160	H	7-diethylamino
1161	H	7-dimethylamino
1162	H	7-dimethylamino
1163	H	7-methoxy
1164	H	7-methoxy
1165	H	7-trimethylammonium iodide
1166	H	7-trimethylammonium iodide
1167	H	7-dimethylamino
1168	H	7-trimethylammonium iodide
1169	H	8-dimethylamino
1170	H	7-ethylpropylamino
1171	H	7-dimethylamino
1172	H	7-methoxy

Compound Number	R ^{SB}	(R ⁶) _m
1173	H	7-ethylpropylamino
1174	H	7-phenyl
1175	H	7-methylsulfonyl
1176	H	9-fluoro
1177	H	7-butylmethylamino
1178	H	7-dimethylamino
1179	H	8-methoxy
1180	H	7-trimethylammonium iodide
1181	H	7-butylmethylamino
1182	H	7-methoxy
1183	H	7-fluoro
1184	H	7-fluoro; 9-fluoro
1185	H	7-fluoro
1186	H	7-fluoro; 9-fluoro
1187	H	7-methyl
1188	H	7-trimethylammonium iodide
1189	H	7-trimethylammonium iodide
1190	H	7-bromo
1191	H	7-hydroxy
1192	H	7-hydroxy
1193	H	7-dimethylamino
1194	H	7-dimethylamino
1195	H	7-(4'-methylpiperazin-1-yl)
1196	H	7-methoxy
1197	H	7-(N-methylformamido)
1198	H	7-methoxy


Compound Number	R ^{5B}	(R ⁶) _m
1199	H	7-dimethylamino
1200	phenyl	7-dimethylamino
1201	H	7-methyl
1202	H	7-methoxy
1203	H	7-(4'-tert-butylphenyl)
1204	H	7-methoxy
1205	H	7-dimethylamino
1206	H	7-dimethylamino
1207	H	7-dimethylamino
1208	H	7-dimethylamino
1209	H	7-dimethylphenyl
1210	H	7-dimethylamino
1211	H	7-dimethylamino
1212	H	9-(4'-morpholino)
1213	3-fluoro-4-methoxy-phenyl	7-dimethylamino
1214	H	7-(N-methylformamido)
1215	H	9-methylmercapto
1216	H	7-bromo
1217	H	7-dimethylamino
1218	H	9-methylsulfonyl
1219	H	7-dimethylamino
1220	H	7-isopropylamino
1221	H	7-dimethylamino
1222	H	7-ethylamino

Compound Number	R ^{SB}	(R ⁶) _m
1223	H	8-bromo; 7-methylamino
1224	H	7-fluoro
1225	H	7-dimethylamino
1226	H	7-bromo
1227	H	7-(tert-butylamino)
1228	H	8-bromo; 7-dimethylamino
1229	H	7-dimethylamino
1230	H	9-dimethylamino; 7-fluoro
1231	H	7-dimethylamino
1232	H	9-dimethylamino
1233	H	7-dimethylamino
1234	H	7-dimethylamino
1235	H	7-dimethylamino
1236	H	7-dimethylamino
1237	H	7-dimethylamino
1238	H	7-dimethylamino
1239	H	7-dimethylamino
1240	H	7-dimethylamino
1241	H	7-dimethylamino
1242	H	7-dimethylamino
1243	H	7-dimethylamino
1244	H	7-(1'-methylhydrazido)
1245	H	7-dimethylamino

Compound Number	R ^{SB}	(R ⁶) _m
1246	H	7-dimethylamino
1247	H	7-dimethylamino
1248	H	7-dimethylamino
1249	H	7-dimethylamino
1250	H	7-dimethylamino
1251	H	7-dimethylamino
1252	H	7-dimethylamino
1253	H	7-dimethylamino
1254	H	7-dimethylamino
1255	H	7-dimethylamino
1256	H	7-dimethylamino
1257	H	8-bromo; 7-dimethylamino
1258	H	9-(tert-butylamino)
1259	phenyl	7-dimethylamino
1260	H	7-dimethylamino
1261	H	7-dimethylamino
1262	H	7-dimethylamino
1263	H	7-bromo
1264	H	7-isopropylamino
1265	H	9-isopropylamino
1266	H	7-dimethylamino
1267	H	7-carboxy, methyl ester
1268	H	7-dimethylamino
1269	H	7-dimethylamino
1270	H	7-dimethylamino
1271	H	7-dimethylamino

Compound Number	R ^{SB}	(R ^S) _m
1272	H	7-dimethylamino
1273	H	7-dimethylamino
1274	H	7-dimethylamino
1275	H	7-dimethylamino
1276	H	7-dimethylamino
1277	H	7-dimethylamino
1278	H	7-dimethylamino
1279	H	7-dimethylamino
1280	H	7-dimethylamino
1281	H	7-dimethylamino
1282	H	7-trimethylammonium iodide
1283	H	7-dimethylamino
1284	H	9-ethylamino
1285	H	7-dimethylamino
1286	H	7-dimethylamino
1287	H	7-dimethylamino
1288	H	7-dimethylamino
1289	H	7-dimethylamino
1290	H	7-dimethylamino
1291	H	7-dimethylamino
1292	H	7-dimethylamino
1293	H	7-dimethylamino
1294	H	7-dimethylamino
1295	H	7-dimethylamino
1296	H	7-dimethylamino
1297	H	7-dimethylamino

Compound Number	R ^{SB}	(R ⁶) _m
1298	H	7-dimethylamino
1299	H	7-dimethylamino
1300	phenyl	7-dimethylamino
1301	H	7-trimethylammonium iodide
1302	H	9-hydroxy
1303	H	7-dimethylamino
1304	H	7-tert-butylamino
1305	H	9-methylamino
1306	H	7-dimethylamino
1307	4-methoxy-phenyl	9-(4'-morpholino)
1308	H	7-dimethylamino
1309	H	9-fluoro
1310	H	7-amino
1311	H	7-(hydroxylamino)
1312	H	8-hexyloxy
1313	H	8-ethoxy
1314	H	7-(hydroxylamino)
1315	H	7-(hexyloxy)
1316	H	8-hydroxy
1317	H	I ⁻
		$\text{CH}_3\text{O}-\text{C}^+ \left[\text{CH}_2\text{CH}_3 \right]_3 \text{N}(\text{CH}_3)_3$

Compound Number	R ^{SB}	(R ⁶) _m
1335	H	7-dimethylamino
1336	H	7-dimethylamino
1337	H	7-dimethylamino
1338	H	7-(4'-methylpiperazinyl)
1339	H	7-dimethylamino
1340	H	7-methyl
1341	H	7-dimethylamino
1342	H	7-(4'-fluorophenyl)
1343	H	7-amino
1344	H	7-dimethylamino
1345	H	7-trimethylammonium iodide
1346	H	 <p>at the 8-position</p>
1347	H	
1348	H	
1349	H	
1350	H	
1351	H	
1352	H	
1353	H	
1354	H	
1355	H	
1356	H	7-dimethylamino
1357	H	7-dimethylamino

Compound Number	R ^{5B}	(R ⁶) _m
1358	H	7-dimethylamino
1359	H	7-dimethylamino
1360	H	7-dimethylamino
1361	H	7-dimethylamino
1362	H	7-dimethylamino
1363	H	7-dimethylamino
1364	H	7-dimethylamino
1365	H	7-dimethylamino
1366	H	7-dimethylamino
1367	H	7-dimethylamino
1368	H	7-dimethylamino
1369	H	7-dimethylamino
1370	H	7-dimethylamino
1371	H	7-dimethylamino
1372	H	7-dimethylamino
1373	H	7-dimethylamino
1374	H	7-dimethylamino
1375	H	7-dimethylamino
1376	H	7-dimethylamino
1377	H	7-dimethylamino
1378	H	7-dimethylamino
1379	H	7-dimethylamino
1380	H	7-dimethylamino
1381	H	7-dimethylamino
1382	H	7-dimethylamino
1383	H	7-dimethylamino

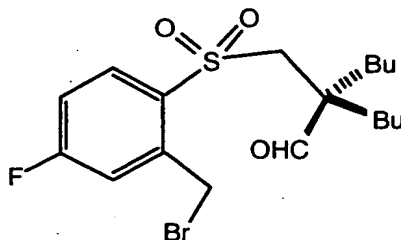
Compound Number	R ^{5B}	(R ⁶) _m
1384	H	7-dimethylamino
1385	H	7-dimethylamino
1386	H	7-dimethylamino
1387	H	7-dimethylamino
1388	H	7-dimethylamino
1389	H	7-dimethylamino
1390	H	7-dimethylamino
1391	H	7-dimethylamino
1392	H	7-dimethylamino
1393	H	7-dimethylamino
1394	H	7-dimethylamino
1395	H	7-dimethylamino
1396	H	7-dimethylamino
1397	H	7-dimethylamino
1398	H	7-dimethylamino
1399	H	7-dimethylamino
1400	H	7-dimethylamino
1401	H	7-dimethylamino
1402	H	7-dimethylamino
1403	H	7-dimethylamino
1404	H	7-dimethylamino
1405	H	7-dimethylamino
1406	H	7-dimethylamino
1407	H	7-dimethylamino
1408	H	7-dimethylamino
1409	H	7-dimethylamino

Compound Number	R ^{5B}	(R ⁶) _m
1410	H	7-dimethylamino
1411	H	7-dimethylamino
1412	H	7-dimethylamino
1413	H	7-dimethylamino
1414	H	7-dimethylamino
1415	H	7-dimethylamino
1416	H	7-dimethylamino
1417	H	7-dimethylamino
1418	H	7-dimethylamino
1419	H	7-dimethylamino
1420	H	7-dimethylamino
1421	H	7-dimethylamino
1422	H	7-dimethylamino
1423	H	7-dimethylamino
1424	H	7-dimethylamino
1425	H	7-dimethylamino
1426	H	7-dimethylamino
1427	H	7-dimethylamino
1428	H	7-dimethylamino
1429	H	7-dimethylamino
1430	H	7-dimethylamino
1431	H	7-dimethylamino
1432	H	7-dimethylamino
1433	H	7-dimethylamino
1434	H	7-dimethylamino
1435	H	7-dimethylamino

Compound Number	R ^{5B}	(R ⁶) _m
1436	H	7-dimethylamino
1437	H	7-dimethylamino
1438	H	7-dimethylamino
1439	H	7-dimethylamino
1440	H	7-dimethylamino
1441	H	7-dimethylamino
1442	H	7-dimethylamino
1443	H	7-dimethylamino
1444	H	7-dimethylamino
1445	H	7-dimethylamino
1446	H	7-methoxy, 8-methoxy
1447	H	7-dimethylamino
1448	H	7-dimethylamino
1449	H	7-dimethylamino
1450	H	7-dimethylamino
1451	H	7-dimethylamino

[911] Example 1395

[912] Dibutyl 4-fluorobenzene dialdehyde



[913] Step 1: Preparation of dibutyl 4-fluoro benzene dialdehyde

[914] To a stirred solution of 17.5 g (123 mmol) of 2,5-difluorobenzaldehyde (Aldrich) in 615 mL of DMSO at ambient temperature was added 6.2 g (135 mmol) of lithium sulfide (Aldrich). The dark red solution was stirred at 75°C for 1.5 hours, or until the starting material was completely consumed, and then 34 g (135 mmol) of dibutyl mesylate aldehyde was added at about 50°C. The reaction mixture was stirred at 75°C for three hours or until the reaction was completed. The cooled solution was poured into water and extracted with ethyl acetate. The combined extracts were washed with water several times, dried (MgSO₄) and concentrated in vacuo. Silica gel chromatographic purification of the crude product gave 23.6 g (59%) of fluorobenzene dialdehyde as a yellow oil: ¹H NMR (CDCl₃) δ 0.87 (t, *J* = 7.05 Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.78 (m, 4H), 3.09 (s, 2H), 7.2-7.35 (m, 1H), 7.5-7.6 (m, 2H), 9.43 (s, 1H), 10.50 (d, *J* = 2.62 Hz, 1H).

[915] Step 2: Preparation of dibutyl 4-fluorobenzyl alcohol

[916] To a solution of 22.6 g (69.8 mmol) of the dialdehyde obtained from Step 1 in 650 mL of THF at -60°C was added 69.8 mL (69.8 mmol) of DIBAL (1M in THF) via a syringe. The reaction mixture was stirred at -40°C for 20 hours. To the cooled solution at -40°C was added sufficient amount of ethyl acetate to quench the excess of DIBAL, followed by 3 N HCl. The mixture was extracted with ethyl acetate, washed with water, dried (MgSO₄), and concentrated in vacuo. Silica gel chromatographic purification of the crude

product gave 13.5 g (58%) of recovered starting material, and 8.1 g (36%) of the desired fluorobenzyl alcohol as a colorless oil: ^1H NMR (CDCl_3) δ 0.88 (t, $J = 7.05$ Hz, 6H), 1.0-1.4 (m, 8H), 1.5-1.72 (m, 4H), 1.94 (br s, 1H), 3.03 (s, 2H), 4.79 (s, 2H), 6.96 (dt, $J = 8.46, 3.02$ Hz, 1H), 7.20 (dd, $J = 9.47, 2.82$ Hz, 1H), 7.42 (dd, $J = 8.67, 5.64$, 1H), 9.40 (s, 1H).

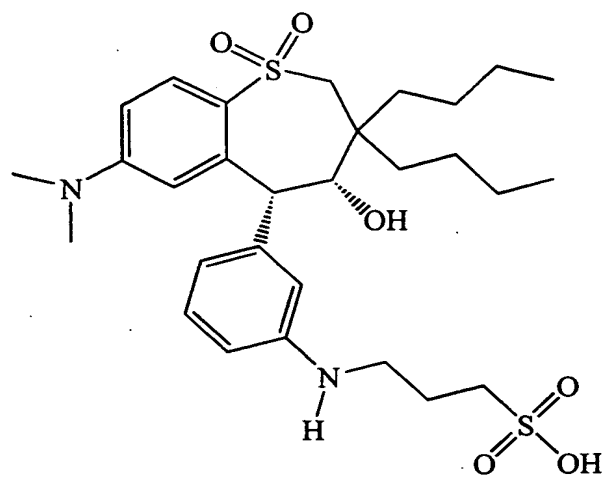
[917] Step 3: Preparation of dibutyl 4-fluorobenzyl bromide

[918] To a solution of 8.1 g (25 mmol) of benzyl alcohol obtained from Step 2 in 100 mL of DMF at -40°C was added 47 g (50 mmol) of bromotriphenylphosphonium bromide (Aldrich). The resulting solution was stirred cold for 30 min, then was allowed to warm to 0°C . To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed a few times with water, dried (MgSO_4), and concentrated *in vacuo*. The mixture was stirred in small amount of ethyl acetate/hexane mixture (1:4 ratio) and filtered through a pad of silica gel, eluting with same solvent mixture. The combined filtrate was concentrated *in vacuo* to give 9.5 g (98%) of the desired product as a colorless oil: ^1H NMR (CDCl_3) δ 0.88 (t, $J = 7.05$ Hz, 6H), 1.0-1.4 (m, 8H), 1.55-1.78 (m, 4H), 3.11 (s, 2H), 4.67 (s, 2H), 7.02 (dt, $J = 8.46, 3.02$ Hz, 1H), 7.15 (dd, $J = 9.47, 2.82$ Hz, 1H), 7.46 (dd, $J = 8.67, 5.64$, 1H), 9.45 (s, 1H).

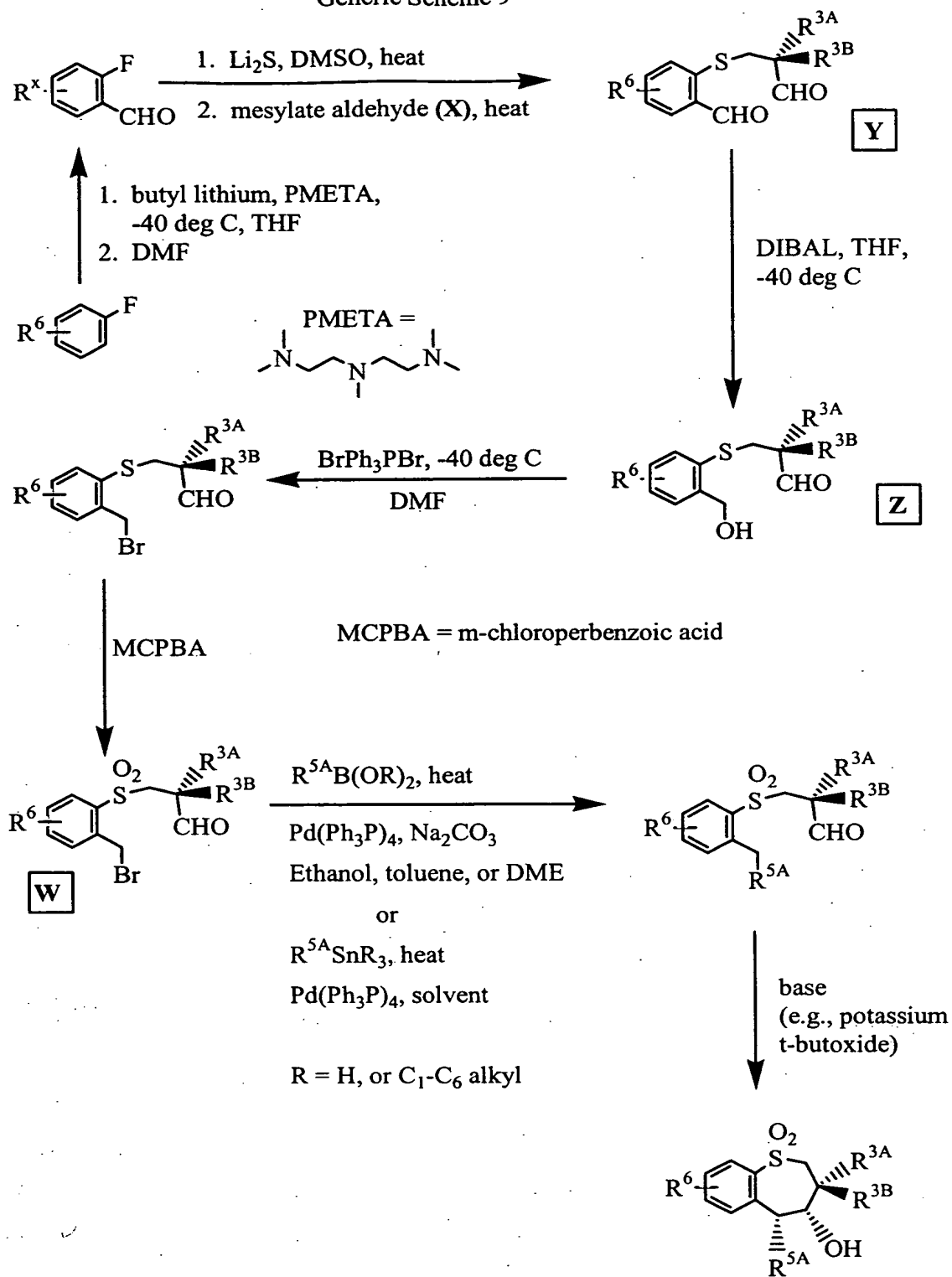
[919] Step 4: Preparation of sulfonyl 4-fluorobenzyl bromide

[920] To a solution of 8.5 g (25 mmol) of sulfide obtained from Step 3 in 200 mL of CH_2Cl_2 at 0°C was added 15.9 g (60 mmol) of mCPBA (64% peracid). The resulting solution was stirred cold for 10 min, then was allowed to stirred ambient temperature for 5 hours. To the mixture was added 10% solution of sodium sulfite and ethyl acetate. The extract was washed several times with saturated Na_2CO_3 , dried (MgSO_4), and concentrated *in vacuo* to give 10.2 g (98%) of the desired product as a colorless oil: ^1H NMR (CDCl_3) δ 0.91 (t, $J = 7.05$ Hz, 6H), 1.03-1.4 (m, 8H), 1.65-1.82 (m, 2H), 1.90-2.05 (m, 2H), 3.54 (s, 2H), 5.01 (s, 2H), 7.04-7.23 (m, 1H), 7.30 (dd, $J = 8.87, 2.42$ Hz, 1H), 8.03 (dd, $J = 8.86, 5.64$, 1H), 9.49 (s, 1H).

[921] Example 1396



Generic Scheme 9

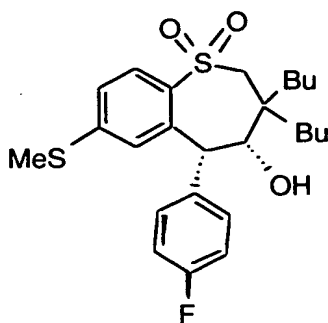


[922] Generic Scheme 9: The nucleophilic substitution of an appropriately substituted 2-fluorobenzaldehyde with lithium sulfide or other nucleophilic sulfide anion in polar solvent (such as DMF, DMA, DMSO ..etc), followed by the addition of dialkyl mesylate aldehyde (X), provided a dialkyl benzene dialdehyde Y. DIBAL reduction of the dialdehyde at low temperature yielded benzyl alcohol monoaldehyde Z. Conversion of benzyl alcohol to benzyl bromide, followed by oxidation of sulfide to sulfone yielded the key intermediate W.

[923] Example 1397

[924] The 7-fluoro, 9-fluoro and 7,9-difluoro analogs of benzothiepine compounds can be reacted with sulfur and nitrogen nucleophiles to give the corresponding sulfur and nitrogen substituted analogs. The following example demonstrates the synthesis of these analogs.

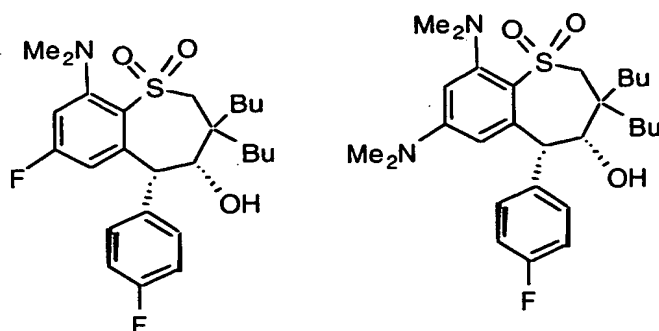
[925] **3,3-Dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.**



[926] A mixture of 0.4 g Of 3,3-dibutyl-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by previously described method, 0.12 g of sodium methanethiolate and 20 ml of DMF was stirred at 50°C for 3 days. An additional 0.1 g of sodium methanethiolate was added to the reaction mixture and the mixture was stirred for additional 20 h at 50°C then was concentrated in vacuo. The residue was triturated with water and extracte wiith ether. The ether extract was dried over MgSO₄ and concentrated

in vacuo to 0.44 g of an oil. Purification by HPLC (10% EtOAc in hexane) gave 0.26 g of needles, mp 164-165.5 °C.

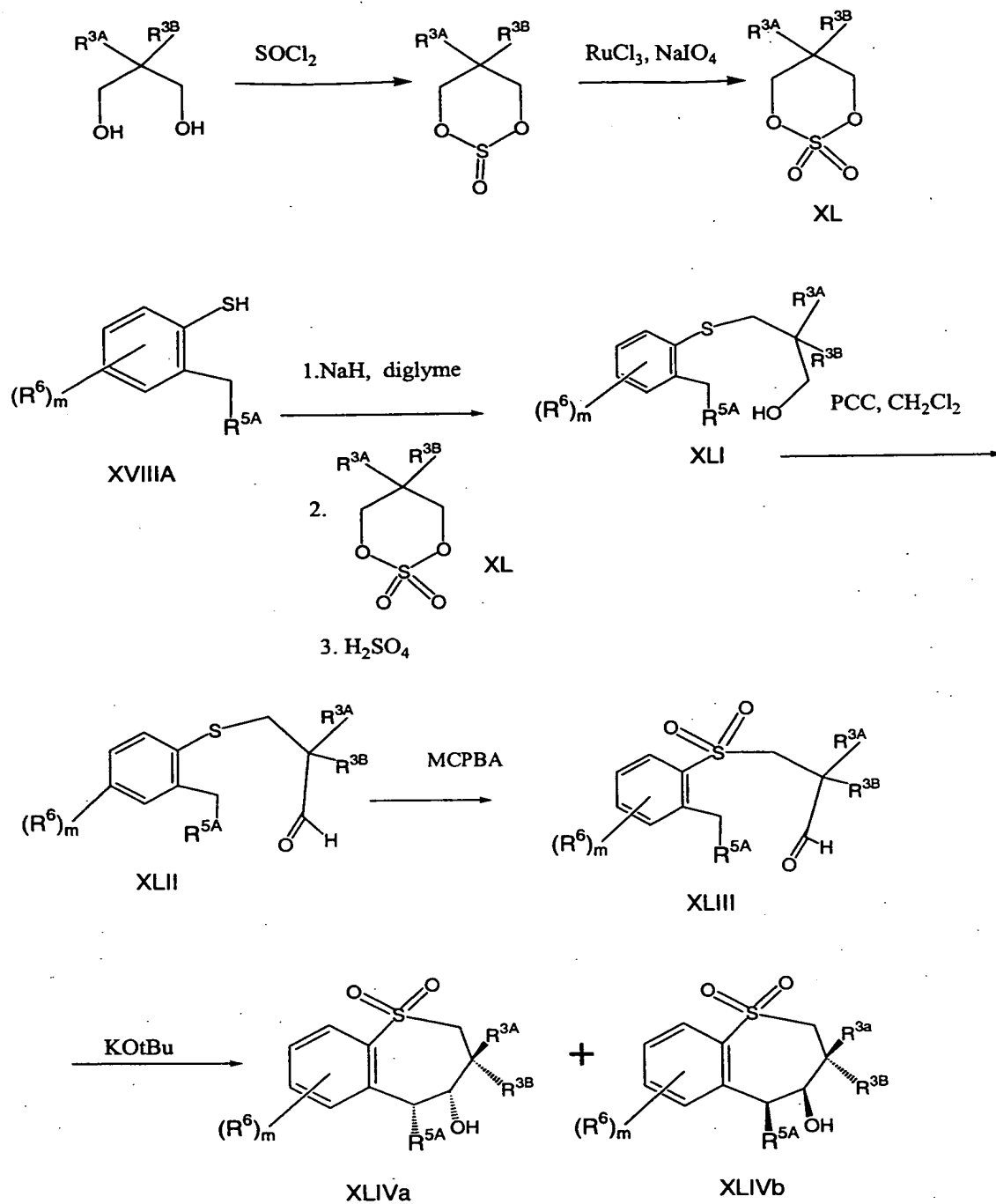
- [927] **3,3-Dibutyl-9-dimethylamino-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide and 7,9-Bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide.**



- [928] A solution of 0.105 g of 3,3-dibutyl-7,9-difluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, prepared by the method described previously, in 20 ml of 2 N dimethylamine in THF was heated at 160°C in a sealed Parr reactor overnight. The reaction mixture was cooled and concentrated in vacuo. The residue was triturated with 25 ml of water and extracted with ether. The ether extract was dried over MgSO₄ and concentrated in vacuo. The residue was purified by HPLC (10% EtOAc in hexane) to give 35 mg of an earlier fraction which was identified as 3,3-dibutyl-9-dimethylamino-7-fluoro-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 480 (M⁺ +1), and 29 mg of a later fraction which was identified as 7,9-bis(dimethylamino)-3,3-dibutyl-5a-(4'-fluorophenyl)-4a-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide, MS (CI) m/e 505 (M⁺ +1).

- [929] The compounds of this invention can also be synthesized using cyclic sulfate (XL, below) as the reagent as shown in the following schemes XI and XII. The following examples describe a procedure for using the cyclic sulfate as the reagent.

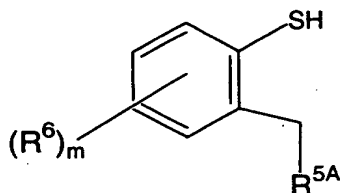
SCHEME 10.



[930] Scheme 10 illustrates yet another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl analogs, starting from the thiophenol XVIII. Thiophenol XVIII can be reacted with cyclic sulfate XL to give the alcohol

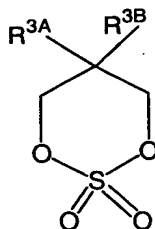
XLI which can be oxidized to yield the aldehyde XLII. Aldehyde XLII itself can be further oxidized to give the sulfone XLIII which can be cyclized to give a stereoisomeric mixture of benzothiepine XLIVa and XLIVb.

- [931] Thiophenol XVIIIA can be prepared according to Scheme 7 as previously discussed and has the following formula:



XVIII A

- [932] wherein R^{5A} , R^6 and m are as previously described in connection with Formulas I-1 to I-24, where similar substituents R^{5A} and R^6 are described. Cyclic sulfate XL can be prepared according to synthetic procedures known in the art and has the following formula:



XL

- [933] wherein R^{3A} and R^{3B} are as previously described in connection with Formulas I-1 to I-24 wherein similar substituents R^{3A} and R^{3B} are described. Preferred for the compounds of formula I. Preferably, R^1 and R^2 are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R^1 and R^2 are n-butyl.

- [934] In the process of Scheme XI, thiophenol XVIIIA is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as methoxyethyl ether. While the reaction conditions such as temperature and time are not narrowly critical, the reaction preferably is

allowed to proceed at about room temperature for about two hours. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield can be improved by using about 1.01 to 1.3 equivalents of cyclic sulfate XL for each equivalent of thiophenol XVIIIA present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of thiophenol XVIIIA present.

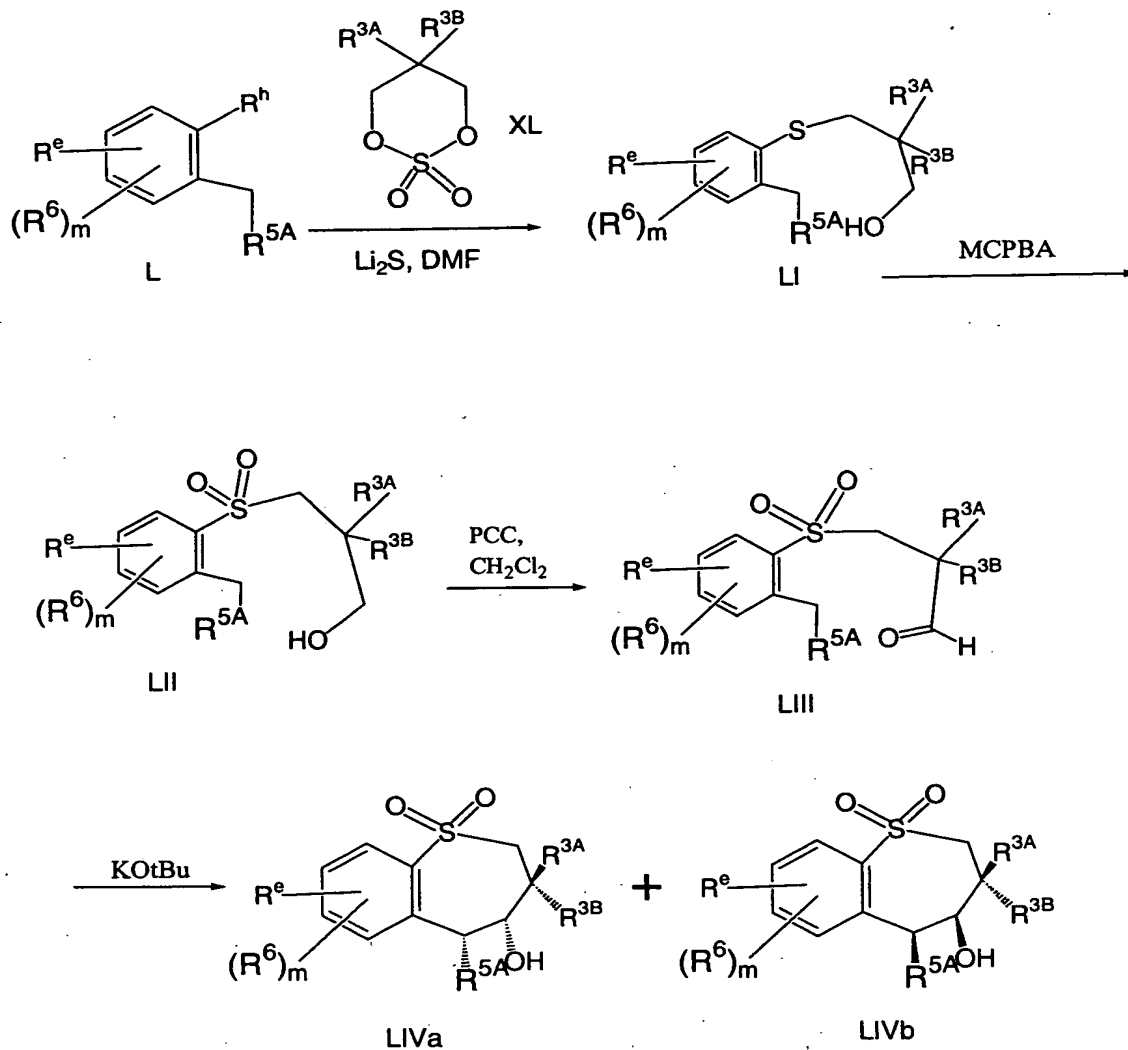
[935] In the process of the invention, thiophenol XVIIIA also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing thiophenol XVIIIA prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the hydrogen atom from the mercaptan group attached to the benzene ring of thiophenol XVIIIA. The resulting sulfur anion of the thiophenol then reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the thiophenol then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group.

[936] The abstracting agent generally is a base having a pH greater than about 10. Preferably, the base is an alkali metal hydride such as sodium hydride, lithium hydride or potassium hydride; more preferably, the base is sodium hydride. A slight excess of abstracting agent is preferred relative to thiophenol XVIIIA. Reaction time and yield is improved by using about 1.0 to about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIA present. More preferably, this ratio is about 1.1 equivalents of abstracting agent for each equivalent of thiophenol XVIIIA present.

[937] The sulfate group of the intermediate product of the reaction of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield alcohol XLI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid.

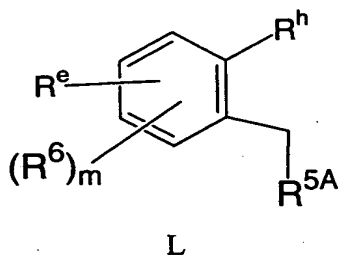
- [938] The several reactions involving thiophenol XVIIIA, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need for isolation of any of the intermediates produced.
- [939] Alcohol XLI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to aldehyde XLII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.
- [940] Aldehyde XLII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde XLIII. Preferably, the oxidizing agent is metachloroperbenzoic acid.
- [941] Sulfone-aldehyde XLIII likewise is isolated by conventional methods and then cyclized to form the stereoisomeric benzothiepines XLIVa and XLIVb. The cyclizing agent preferably is a base having a pH between about 8 and about 9. More preferably, the base is an alkoxide base, and still more preferably, the base is potassium tert-butoxide.
- [942] The two oxidation steps of Scheme 10 can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield a sulfone-alcohol which is then oxidized to yield a sulfone-aldehyde.

SCHEME 11

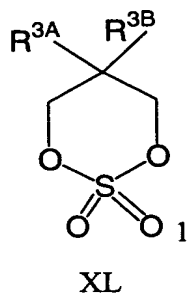


[943] Scheme 11 illustrates still another route to benzothiepine-1,1-dioxides, particularly 3,3-dialkyl analogs, starting from the halobenzene **L**. Halobenzene **L** can be reacted with cyclic sulfate **XL** disclosed above to give the alcohol **LI** which can be oxidized to yield the sulfone-alcohol **LII**. Sulfone-alcohol **LII** itself can be further oxidized to give the sulfone-aldehyde **LIII** which can be cyclized to give a stereoisomeric mixture of benzothiepine **LIVa** and **LIVb**.

[944] Halobenzene L (which is commercially available or can be synthesized from commercially available halobenzenes by one skilled in the art) has the following formula:



[945] wherein R^{5A} , R^6 , and m are as previously described in connection with compounds of Formulas I-1 to I-24, where substituents R^{5A} and R^6 are described. R^h is a halogen such as chloro, bromo, fluoro or iodo; and R^e is an electron withdrawing group at the ortho or para position of the halobenzene, and is preferably a p-nitro or o-nitro group. Cyclic sulfate XL can be prepared as set forth in Scheme XI and can have the following formula:



[946] wherein R^{3A} and R^{3B} are as previously described in connection with compounds of Formulas I-1 to I-24, where substituents R^{3A} and R^{3B} are described. Preferably, R^{3A} and R^{3B} are alkyl; more preferably, they are selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl; and still more preferably, R^{3A} and R^{3B} are n-butyl.

[947] In the process of Scheme 11, halobenzene L is initially reacted with cyclic sulfate XL. This reaction preferably is conducted in an aprotic solvent such as dimethyl formamide or N:N-dimethylacetamide, and more preferably, in dimethyl formamide. Although the reaction conditions such as temperature

and time are not narrowly critical, the reaction preferably is allowed to proceed at between about 70°C and about 90°C for about 8 to 12 hours. More preferably, the reaction temperature is maintained at about 80°C. The reaction preferably employs an approximately stoichiometric ratio of the starting materials, with a slight excess of cyclic sulfate XL being preferred. Reaction time and yield is improved by using about 1.1 to 1.3 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present. More preferably, this ratio is about 1.1 equivalents of cyclic sulfate XL for each equivalent of halobenzene L present.

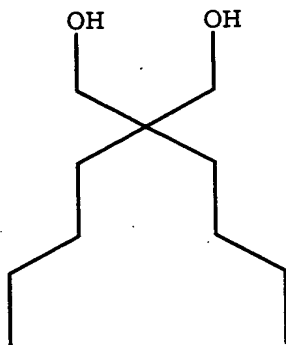
[948] In the above-noted process in connection with the claimed invention, halobenzene L also is treated with an abstracting agent. The abstracting agent can be added to the solvent containing halobenzene L prior to, concurrently with, or after the addition of cyclic sulfate XL. Without being held to a particular theory, it is believed the abstracting agent removes the halogen atom attached to the benzene ring of halobenzene L and replaces that atom with a divalent sulfur atom. The resulting sulfur anion reacts with cyclic sulfate XL to open the sulfate ring. The sulfur anion of the halobenzene then bonds with a terminal carbon atom of the open ring sulfate. The terminal group at the unbonded end of the open ring sulfate is the sulfate group. The abstracting agent generally is a dialkali metal sulfide, and preferably it is dilithium sulfide. A slight excess of the abstracting agent is preferred relative to halobenzene L. Reaction time and yield is improved by using about 1.01 to 1.3 equivalents of abstracting agent for each equivalent of halobenzene L present. More preferably, this ratio is about 1.05 equivalents of abstracting agent for each equivalent of halobenzene L present.

[949] The sulfate group of the product of the reaction of thiophenol XVIIIA with cyclic sulfate XL is then removed, preferably by hydrolysis, to yield a mixture of an ester and alcohol LI. Suitable hydrolyzing agents include mineral acids, particularly hydrochloric acid and sulfuric acid. The ester is then converted to alcohol LI by treatment with an alkali metal hydroxide, preferably sodium hydroxide.

- [950] The several reactions involving halobenzene L, cyclic sulfate XL, the abstracting agent and the hydrolyzing agent can take place in situ without the need to isolate any of the intermediates produced.
- [951] Alcohol LI is then isolated by conventional methods (for example, extraction with aqueous methyl salicylate) and oxidized using standard oxidizing agents to sulfone-alcohol LII. Preferably, the oxidizing agent is metachloroperbenzoic acid. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.
- [952] Sulfone-alcohol LII is then isolated by conventional methods and further oxidized using standard oxidizing agents to sulfone-aldehyde LIII. Preferably, the oxidizing agent is sulfur trioxide or pyridinium chlorochromate, and more preferably, it is pyridinium chlorochromate. The reaction is conducted in a suitable organic solvent such as methylene chloride or chloroform.
- [953] Sulfone-aldehyde XLIII is then converted to the desired benzothiepine-1,1-dioxides according to the procedure previously set forth in Scheme 10.
- [954] The two oxidation steps can be reversed without adversely affecting the overall reaction. Alcohol XLI can be oxidized first to yield an aldehyde which is then oxidized to yield a sulfone-aldehyde.
- [955] Use of the cyclic sulfate reagent instead of a mesylate reagent in Schemes 10 and 11 improves the overall yield and avoids many of the purification difficulties encountered relative to those reaction schemes proceeding through a mesylate intermediate. Overall yields are significantly improved when a cyclic sulfate is used instead of a mesylate reagent. In addition, chromatographic separation of the intermediate product of the cyclic sulfate coupling step of the reaction is not necessary. For example, in Schemes XI and XII the intermediate is a water soluble alkali metal salt and the impurities can be removed by extraction with ether. The intermediate is then hydrolyzed to the desired alcohol.

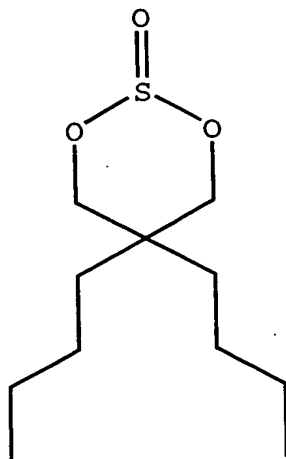
[956] Example Corresponding to Scheme 10:

[957] **Step 1: Preparation of 2,2-dibutyl-1,3-propanediol:**



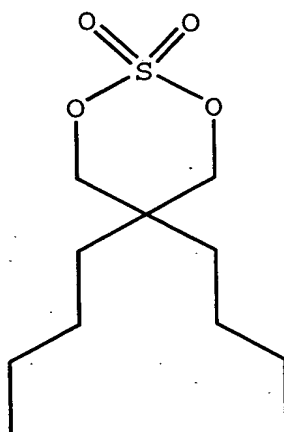
[958] Lithium aluminum hydride (662 ml, 1.2 equivalents, 0.66 mol) in 662 mL of 1M THF was added dropwise to a stirred solution of dibutyl-diethylmalonate (150 g, 0.55 mol) (Aldrich) in dry THF (700ml) while maintaining the temperature of the reaction mixture at between about -20°C to about 0°C using an acetone/dry ice bath. The reaction mixture was then stirred at room temperature overnight. The reaction was cooled to -20°C and 40 ml of water, 80 ml of 10% NaOH and 80 ml of water were successively added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated under vacuum to give 98.4 g (yield 95%) of the diol as an oil. Proton NMR, carbon NMR and MS confirmed the product.

[959] **Step 2: Dibutyl-cyclic-sulfite:**



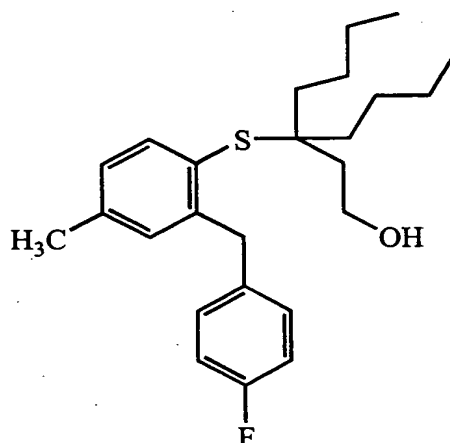
[960] A solution of the dibutyl-diol of step 1 (103 g, 0.5478 mol) in anhydrous methylene chloride (500 ml) and triethylamine (221 g, 4 equivalents, 2.19 mol) was stirred at 0°C under nitrogen. Thionyl chloride (97.78 g, 0.82 mol) was added dropwise to the mixture. Within 5 minutes the solution turned to yellow and then to black when the addition was completed within about half an hour. The reaction was completed within 3 hours (gas chromatography confirmed no starting material was left). The mixture was washed with ice water twice, and brine twice. The organic phase was dried over magnesium sulphate and concentrated under vacuum to give 128 g (yield 100%) of the dibutyl-cyclic-sulfite as a black oil. NMR and MS were consistent with the product.

[961] **Step 3: Dibutyl-cyclic sulfate:**



[962] To a solution of the dibutyl-cyclic-sulfite of step 2 (127.5 g, 0.54 mol) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium(III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. Gas chromatography confirmed there was no starting material left. The mixture was extracted once with 300 ml of ether and three times with brine. The organic phase was dried over magnesium sulphate and passed through celite. The filtrate was concentrated under vacuum and gave 133 g (yield 97.8%) of the dibutyl-cyclic-sulfate as an oil. Proton NMR, carbon NMR and MS confirmed the product.

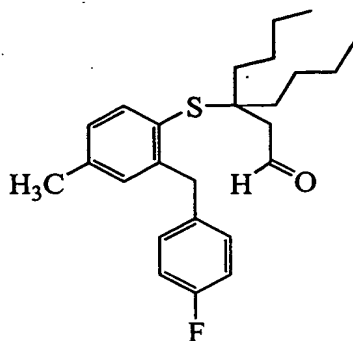
[963] Step 4: 2-[(2-4'-fluorobenzyl-4-methylphenylthio) methyl]-2-butylhexanol:



[964] A 60% oil dispersion of sodium hydride (0.27 g, 6.68 mmole) was washed with hexane. The hexane was decanted and 20 ml of methoxyethyl ether was added to the washed sodium hydride and cooled in an ice bath. A mixture of diphenylmethane thiophenol (1.55 g, 6.68 mmole) in 10 ml of methoxyethyl ether was added dropwise over a period of 15 minutes. A mixture of the dibutyl-cyclic-sulfate of step 3 (2.17 g, 8.66 mmole) in 10 ml of methoxyethyl ether was then added. The resulting mixture was stirred for 30 minutes at 0°C and 1 hour at room temperature under nitrogen. Gas chromatography confirmed there was no thiol left. The solvent was evaporated and washed with water and ether two times. The water layer was separated and 20 ml of

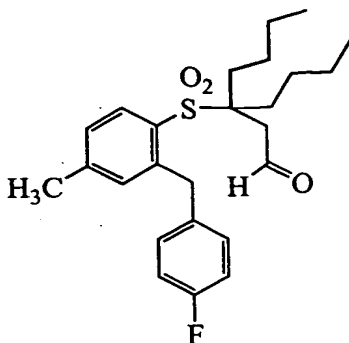
10% NaOH was added. This aqueous mixture was boiled for 30 minutes, cooled, acidified with 6N HCl, and boiled for 10 minutes. The mixture was cooled and extracted with ether. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum to give 2.47 g (yield 92.5%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

[965] **Step 5:** 2-[(2-4'-fluorobenzyl-4-methylphenylthio)methyl]-2-butylhexanal:



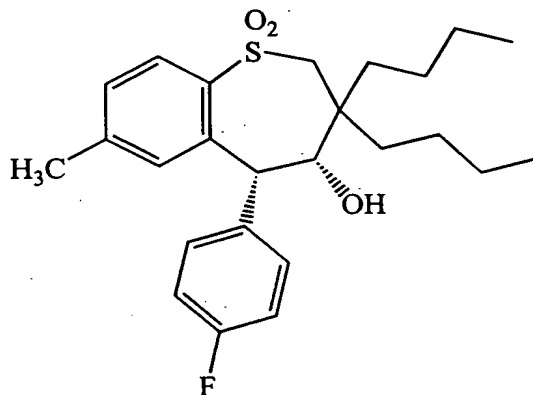
[966] To a solution of the hexanol of step 4 (2 g, 4.9 mmole) in 40 ml of methylene chloride cooled in an ice bath under nitrogen was added pyridinium chlorochromate (2.18 g, 9.9 mmole). The reaction mixture was stirred for 3 hours and filtered through silica gel. The filtrate was concentrated under vacuum to give 1.39 g (yield 70%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

[967] **Step 6:** 2-[(2-4'-fluorobenzyl-4-methylphenylsulfonyl) methyl]-2-butylhexanal



[968] To a solution of the hexanal of step 5 (0.44 g, 1.1 mmole) in 20 ml of methylene chloride cooled by an ice bath under nitrogen was added 70 % metachloroperbenzoic acid (0.54 g, 2.2 mmole). The reaction mixture was stirred for 18 hours and filtered. The filtrate was washed successively with 10% NaOH(3X), water, and brine, dried over magnesium sulphate, and concentrated under vacuum to give 0.42 g (yield 90%) of the hexanal as an oil. Proton NMR, carbon NMR and MS confirmed the product.

[969] Step 7: **Cis-3,3-dibutyl-7-methyl-5-(4'-fluoro-phenyl)-2,3,4,5-tetrahydrobenzothiiepine-1,1-dioxide:**

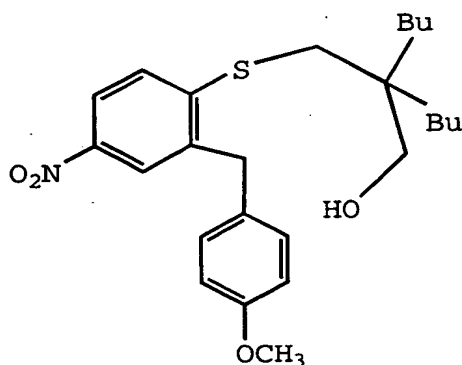


[970] A mixture of the hexanal of step 6 (0.37 g, 0.85 mmole) in 30 ml of anhydrous THF was stirred in an ice bath at a temperature of about 0°C. Potassium-tert-butoxide (102 mg, 0.85 mmole) was then added. After 3 hours thin layer chromatography confirmed the presence of the product and a small amount of the starting material. The crude reaction mixture was acidified with 10% HCl, extracted with ether, washed successively with water and brine, dried with MgSO₄, and concentrated under vacuum. This concentrate was purified by

HPLC (10% EtOAc-Hexane). The first fraction came as 0.1 g of the starting material in the form of an oil. The second fraction yielded 0.27 g (75% yield) of the desired benzothiepine as a white solid. Proton NMR, carbon NMR and MS confirmed the product. (M+H=433).

[971] Example Corresponding to Scheme 11

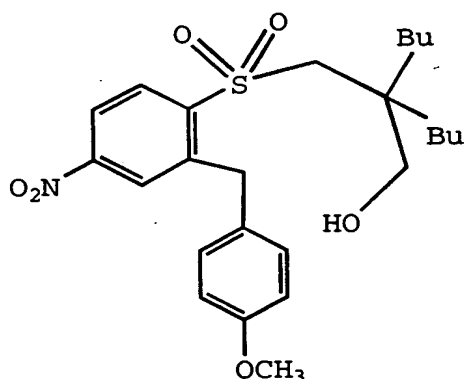
[972] **Step 1:** 2-[(2-4'-methoxybenzyl-4-nitrophenylthio)-methyl]-2-butylhexanol:



[973] Chlorodiphenylmethane (10g) was dissolved in 25 ml of DMF and lithium sulfide [1.75 g, 1.05 equivalents] was added. The solution color changed to red. The reaction mixture was heated at 80°C overnight. The solution was cooled to 0°C and dibutyl-cyclic-sulfate (9.9g; prepared as set forth in Step 3 of the Scheme XI examples) in 10 ml of DMF was added and stirred at room temperature overnight. The solvent was evaporated and washed successively with water and ether (three times). The water layer was separated and 40 ml of concentrated sulfuric acid was added and the reaction mixture boiled overnight. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum. The product was boiled with 3M of NaOH for 1 hour. The mixture was cooled and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20% ethyl acetate and hexane, and concentrated under vacuum to

give 11.9 g (yield 74%) of the hexanol as an oil. Proton NMR, C13-NMR and MS confirmed the product.

[974] Step 2: 2-[2-4'-methoxybenzyl-4-nitrophenylthio)-methyl]-2-butylhexanal:



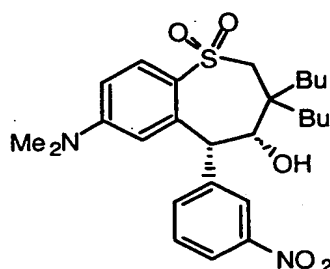
[975] To a solution of the hexanol of step 1 (6 g, 13 mmole) in 50 ml methylene chloride cooled in ice bath under nitrogen was added 70% MCPBA (8.261 g, 33 mmole). The reaction was stirred for 18 hours at room temperature and filtered. The filtrate was washed successively with 10% NaOH (3X), water and brine, dried over magnesium sulphate, and concentrated under vacuum. The concentrate was dissolved in methylene chloride, filtered through silica gel, eluted with 20% ethyl acetate and hexane, and concentrated under vacuum to give 5 g (yield 77.7%) of the hexanal as a white solid, MP 58-60°C. Proton NMR, C13-NMR and MS confirmed the product.

[976] Example 1398

[977] Step 1. Preparation of 2

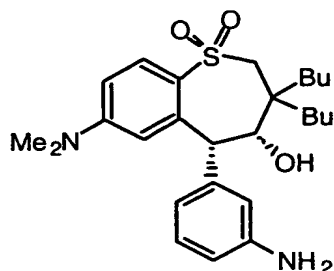
Purification by silica gel chromatography through a 100 ml plug using CH_2Cl_2 as eluent yielded 4.3 g (90%) of **3** as a pale yellow foam. ^1H NMR (CDCl_3) δ 0.93 (t, $J = 7.25$ Hz, 6H), 1.00-1.55 (m, 8H), 1.59-1.74 (m, 3H), 2.15-2.95 (m, 1H), 3.16 (q_{AB}, $J_{AB} = 15.0$ Hz, $\Delta V = 33.2$ Hz, 2H), 4.17 (d, $J = 6.0$ Hz, 1H), 5.67 (s, 1H), 6.34 (dd, $J = 9.6$ and 3.0 Hz, 1H), 7.08 (dt, $J = 8.5$ and 2.9 Hz, 1H), 7.64 (t, $J = 8.1$ Hz, 1H), 7.81 (d, $J = 8.7$ Hz, 1H), 8.13 (dd, $J = 9.9$ and 3.6 Hz, 1H), 8.23-8.30 (m, 1H), 8.44 (s, 1H). MS(FABH⁺) m/e (relative intensity) 464.5 (100), 446.6 (65). HRMS calculated for $\text{M}+\text{H}$ 464.1907. Found 464.1905.

[981] Step 4. Preparation of 4



[982] To a cooled (0°C) solution of 4.3 g (9.3 mmol) of **3** in 30 ml THF contained in a stainless steel reaction vessel was added 8.2 g dimethyl amine (182 mmol). The vessel was sealed and heated to 110°C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-2000) using an ethyl acetate/hexanes gradient (10-40% ethyl acetate) gave 4.0 g (88%) of **4** as a yellow solid. ^1H NMR (CDCl_3) δ 0.80-0.95 (m, 6H), 0.96-1.53 (m, 8H), 1.60-1.69 (m, 3H), 2.11-2.28 (m, 1H), 2.79 (s, 6H), 3.09 (q_{AB}, $J_{AB} = 15.0$ Hz, $\Delta V = 45.6$ Hz, 2H), 4.90 (d, $J = 9.0$ Hz, 1H), 5.65 (s, 1H), 5.75 (d, $J = 2.1$ Hz, 1H), 6.52 (dd, $J = 9.6$ and 2.7 Hz, 1H), 7.59 (t, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 7.80$ Hz, 1H), 7.89 (d, $J = 9.0$ Hz, 1H), 8.20 (dd, $J = 8.4$ and 1.2 Hz, 1H), 8.43 (s, 1H). MS(FABH⁺) m/e (relative intensity) 489.6 (100), 471.5 (25). HRMS calculated for $\text{M}+\text{H}$ 489.2423. Found 489.2456.

[983] Step 5. Preparation of 5



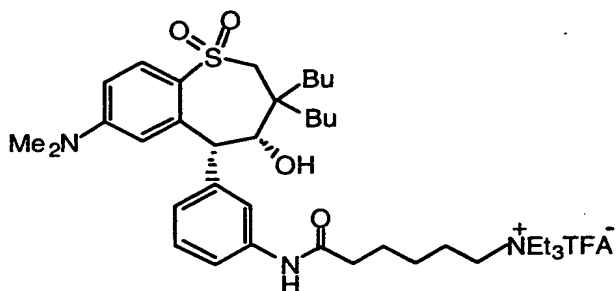
[984] To a suspension of 1.0 g (2.1 mmol) of 4 in 100 ml ethanol in a stainless steel Parr reactor was added 1 g 10% palladium on carbon. The reaction vessel was sealed, purged twice with H₂, then charged with H₂ (100 psi) and heated to 45°C for six hours. The reaction vessel was cooled to ambient temperature and the contents filtered to remove the catalyst. The filtrate was concentrated in vacuo to give 0.9 g (96%) of 5. ¹H NMR (CDCl₃) δ 0.80-0.98 (m, 6H), 1.00-1.52 (m, 10H), 1.52-1.69 (m, 1H), 2.15-2.29 (m, 1H), 2.83 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.1 Hz, DV = 44.2 Hz, 2H), 3.70 (s, 2H), 4.14 (s, 1H), 5.43 (s, 1H), 6.09 (d, J = 2.4 Hz, 1H), 6.52 (dd, J = 12.2 and 2.6 Hz, 1H), 6.65 (dd, J = 7.8 and 1.8 Hz, 1H), 6.83 (s, 1H), 6.93 (d, J = 7.50 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H). MS(FABH⁺) m/e (relative intensity) 459.7 (100). HRMS calculated for M+H 459.2681. Found 459.2670.

[985] Step 6. Preparation of 6

[986] To a solution of 914 mg (2.0 mmol) of 5 in 50 ml THF was added 800 mg (4.0 mmol) 5-bromovaleroyl chloride. Next was added 4 g (39.6 mmol) TEA. The reaction was stirred 10 minutes, then partitioned between ethyl acetate and brine. The organic layer was dried (MgSO₄) and concentrated in vacuo. Purification by silica gel chromatography through a 70 ml MPLC column using a gradient of ethyl acetate(20-50%) in hexane as eluent yielded 0.9 g (73%) of 6 as a pale yellow oil. ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.53 (m, 10H), 1.53-1.68 (m, 1H), 1.80-2.00 (m, 4H), 2.12-2.26 (m, 4H), 2.38 (t, J = 6.9 Hz, 2H), 2.80 (s, 6H), 3.07 (q_{AB}, J_{AB} = 15.6 Hz, DV = 40.4 Hz, 2H), 3.43 (t, J = 6.9 Hz, 2H), 4.10 (s, 1H), 5.51 (s, 1H), 5.95 (d, J = 2.4 Hz,

1H), 6.51 (dd, $J = 9.3$ and 2.7 Hz, 1H), 7.28 (s, 1H), 7.32-7.41 (m, 2H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.90 (d, $J = 9.0$ Hz, 1H).

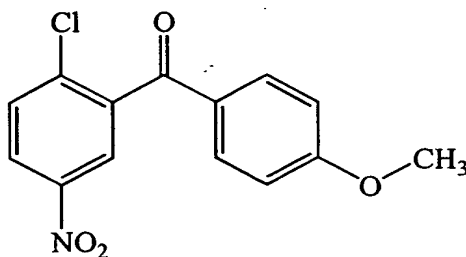
[987] Step 7. Preparation of 7

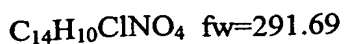


[988] To a solution of 0.9 g (1.45 mmol) of 6 in 25 ml acetonitrile add 18 g (178 mmol) TEA. Heat at 55°C for 16 hours. The reaction mixture was cooled to ambient temperature and concentrated in vacuo. Purification by reverse-phase silica gel chromatography (Waters Delta Prep 3000) using an acetonitrile /water gradient containing 0.05% TFA (20-65% acetonitrile) gave 0.8 g (73%) of 7 as a white foam. ^1H NMR (CDCl_3) δ 0.80-0.96 (m, 6H), 0.99-1.54 (m, 19H), 1.59-1.84 (m, 3H), 2.09-2.24 (m, 1H), 2.45-2.58 (m, 2H), 2.81 (s, 6H), 3.09 (q_{AB}, $J_{AB} = 15.6$ Hz, DV = 18.5 Hz, 2H), 3.13-3.31 (m, 8H), 4.16 (s, 1H), 5.44 (s, 1H), 6.08 (d, $J = 1.8$ Hz, 1H), 6.57 (dd, $J = 9.3$ and 2.7 Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 8.4$ Hz, 1H), 7.56 (d, $J = 8.4$ Hz, 1H), 7.74 (s, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 9.22 (s, 1H). HRMS calcd 642.4304; observed 642.4343.

[989] Example 1398a

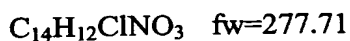
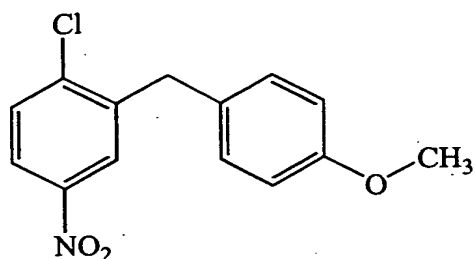
[990] Step 1





- [991] In an inert atmosphere, weigh out 68.3 gms phosphorus pentachloride (0.328mole Aldrich 15,777-5) into a 2-necked 500ml round bottom flask. Fit flask with a N₂ inlet adapter and suba seal. Remove from inert atmosphere and begin N₂ purge. Add 50mls anhydrous chlorobenzene (Aldrich 28,451-3) to the PCl₅ via syringe and begin stirring with magnetic stir bar.
- [992] Weigh out 60 gms 2-chloro-5-nitrobenzoic acid (0.298 mole Aldrich 12,511-3). Slowly add to the chlorobenzene solution while under N₂ purge. Stir at room temperature overnight. After stirring at room temperature for ~20hrs, place in oil bath and heat at 50°C for 1hr. Remove chlorobenzene by high vacuum. Wash residue with anhydrous hexane. Dry acid chloride wt=61.95gms. Store in inert and dry atmosphere.
- [993] In inert atmosphere, dissolve acid chloride with 105mls anhydrous anisole (0.97 mole Aldrich 29,629-5). Place solution in a 2-necked 500ml round bottom flask.
- [994] Weigh out 45.1gms aluminum chloride (0.34 moles Aldrich 29,471-3) and place in a solid addition funnel. Fit reaction flask with addition funnel and a N₂ inlet adapter. Remove from inert atmosphere. Chill reaction solution with ice bath and begin N₂ purge. Slowly add AlCl₃ to chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight .
- [995] Quench reaction by pouring into a solution of 300 mls 1N HCl and ice. Stir 15 min. Extract twice with ether. Combine organic layers and extract twice with 2% NaOH, then twice with deionized H₂O. Dry with MgSO₄, filter and rotovap to dryness. Remove anisole by high vacuum. Crystalize product from 90% ethanol 10% ethyl acetate. Dry on vacuum line. Wt=35.2gms. Yield 41%. Obtain NMR and mass spec (m/z=292).

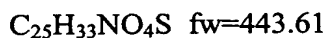
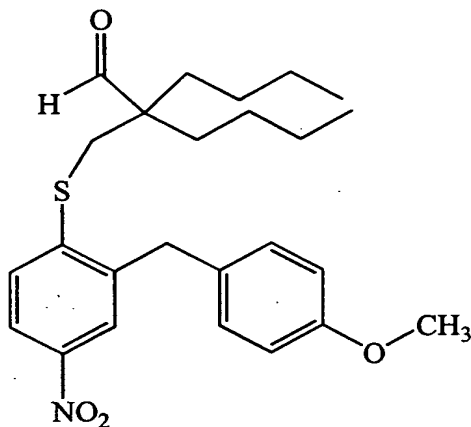
[996] Step 2



- [997] Dissolve 38.10gms (0.131 moles) of the benzophenone from step 1 in 250mls anhydrous methylene chloride. Place in a 3 liter flask fitted with N_2 inlet, addition funnel and stopper. Stir with magnetic stir bar. Chill solution with ice bath.
- [998] Prepare a solution of 39.32 gms trifluoromethane sulfonic acid (0.262 mole Aldrich 15,853-4) and 170 mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2 . Stir 5 minutes after addition is complete.
- [999] Prepare a solution of 22.85 gms triethyl silane (0.197mole Aldrich 23,019-7) and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2 . Stir 5 minutes after addition is complete.
- [1000] Prepare a second solution of 39.32 gms trifluoromethane sulfonic acid and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2 . Stir 5 minutes after addition is complete.
- [1001] Prepare a second solution of 22.85 gms triethyl silane and 170mls anhydrous methylene chloride. Place in addition funnel and add dropwise to chilled solution under N_2 . After all additions are made allow to slowly warm to room temperature overnight. Stir under N_2 overnight.
- [1002] Prepare 1300 mls saturated NaHCO_3 in a 4 liter beaker. Chill with ice bath. While stirring vigorously, slowly add reaction mixture. Stir at chilled temperature for 30 min. Pour into a separatory funnel and allow separation.

Remove organic layer and extract aqueous layer 2 times with methylene chloride. Dry organic layers with MgSO_4 . Crystallize from ethanol. Dry on vacuum line. Dry wt=28.8gms. Confirm by NMR and mass spec ($m/z=278$).

[1003] Step 3

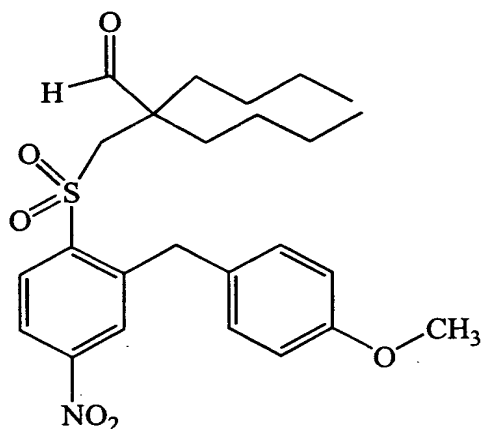


[1004] Dissolve 10.12 gms (0.036 moles) of product 2 with 200 mls anhydrous DMSO. Place in a 500 ml round bottom flask with magnetic stir bar. Fit flask with water condenser, N_2 inlet, and stopper. Add 1.84 gms Li_2S (0.040 moles Aldrich 21,324-1). Place flask in oil bath and heat at 75°C under N_2 overnight then cool to room temperature.

[1005] Weigh out 10.59 gms dibutyl mesylate (0.040 moles). Dissolve with anhydrous DMSO and add to reaction solution. Purge well with N_2 , heat overnight at 80°C .

[1006] Cool to room temperature. Prepare 500 mls of 5% acetic acid in a 2 liter beaker. While stirring, slowly add reaction mixture. Stir 30 min. Extract with ether 3 times. Combine organic layers and extract with water and sat'd NaCl . Dry organic layer with MgSO_4 , filter and rotovap to dryness. Dry oil on vacuum line. Obtain pure product by column chromatography using 95% hexane and 5% ethyl acetate as the mobile phase. Dry wt=7.8 gms. Obtain NMR and mass spec ($m/z=444$).

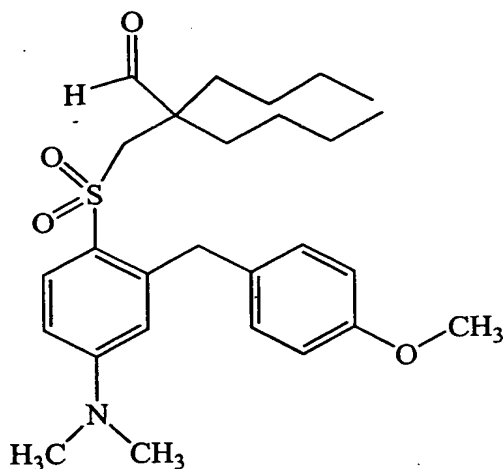
[1007] Step 4



$C_{25}H_{33}NO_6S$ fw=475.61

[1008] Dissolve 9.33 gms (0.021 moles) of product 3 with 120 mls anhydrous methylene chloride. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N_2 inlet and stopper. Chill solution with ice bath under N_2 purge. Slowly add 11.54 gms 3-chloroperbenzoic acid (0.0435 moles, Fluka 25800, ~65%). After addition is complete warm to room temperature and monitor reaction by TLC. Reaction goes quickly to the sulfoxide intermediate but takes 8 hrs to convert to the sulphone. Chill solution overnight in freezer. Filter solid from reaction, extract filtrate with 10% K_2CO_3 . Extract aqueous layer twice with methylene chloride. Combine organic layers and dry with $MgSO_4$. Filter and rotovap to dryness. Obtain pure product by crystallizing from ethanol or isolating by column chromatography. Obtain NMR and mass spec ($m/z=476$).

[1009] Step 5



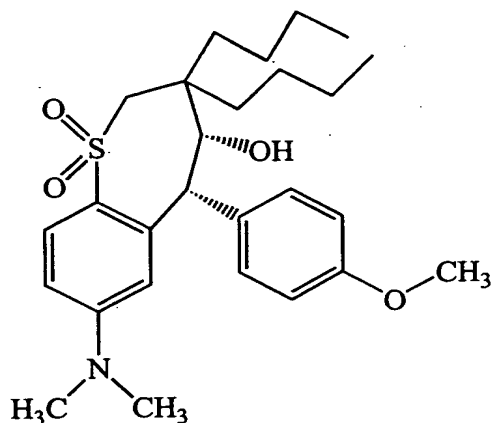
$C_{27}H_{39}NO_4S$ fw=473.68

[1010] Reaction is done in a 300 ml stainless steel Parr stirred mini reactor. Place 9.68 gms (0.0204 moles) of product 4 in reactor base. Add 160 mls ethanol. For safety reasons next two compounds are added in a N_2 atmosphere glove bag. In glove bag, add 15.3 mls formaldehyde (0.204 moles, Aldrich 25,254-9, about 37 wt% in water) and 1.45 gms 10% Pd/Carbon (Aldrich 20,569-9). Seal reactor before removing from glove bag. Purge reactor three times with H_2 . Heat to $55^\circ C$ under H_2 . Run reaction at 200 psig H_2 , $55^\circ C$, and a stir rate of 250 rpm. Run overnight under these conditions.

[1011] Cool reactor and vent H_2 . Purge with N_2 . Check progress of run by TLC. Reaction is a mixture of desired product and intermediate. Filter reaction mixture over a bed of celite washing well with ether. Rotovap and redissolve with ether. Extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line.

[1012] Charge reactor again with same amounts, seal reactor and run overnight under same conditions. After second run all of the material has been converted to the desired product. Cool and vent H_2 pressure. Purge with N_2 . Filter over a bed of celite, washing well with ether. Rotovap to dryness. Dissolve with ether and extract with water. Dry organic layer with $MgSO_4$, filter and rotovap to dryness. Dry on vacuum line. Obtain NMR and mass spec ($m/z=474$).

[1013] Step 6

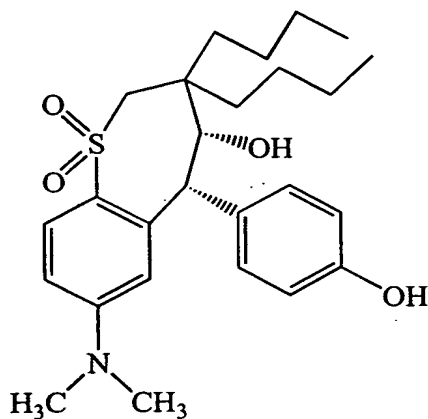


C₂₇H₃₉NO₄S fw=473.68

[1014] Dissolve 8.97 gms (0.0189 mole) of product 5 with 135 mls anhydrous THF.

Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N₂ inlet and stopper. Chill solution with ice/salt bath under N₂ purge. Slowly add 2.55 gms potassium t-butoxide (0.227 mole Aldrich 15,667-1). After addition is complete, continue to stir at -10°C monitoring by TLC. Once reaction is complete, quench by adding 135 mls 10% HCl stirring 10 min. Extract three times with ether. Dry organic layer with MgSO₄, filter and rotovap to dryness. Crystallize from ether. Obtain NMR and mass spec (m/z=474).

[1015] Step 7

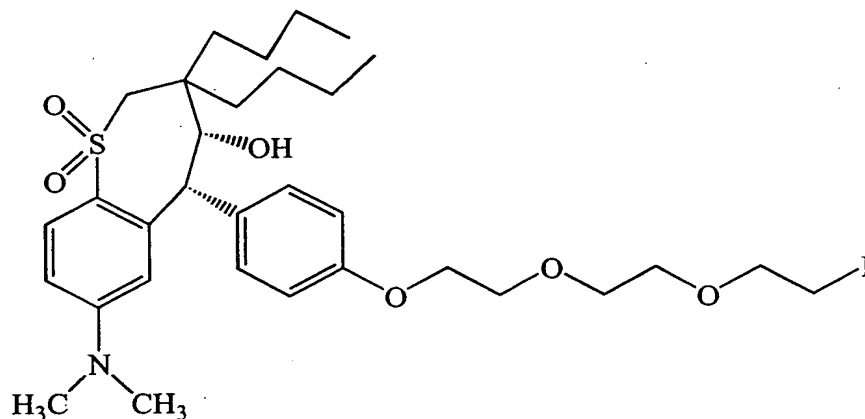


C₂₆H₃₇NO₄S fw=459.65

[1016] Dissolve 4.67 gms (0.01 moles) of product 6 with 100 mls anhydrous chloroform. Place in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N₂ inlet adapter and suba seal. Chill solution with dry ice /acetone bath under a N₂ purge. Slowly add, via syringe, 2.84 mls boron tribromide (0.03 moles Aldrich 20,220-7). Stir at cold temperature for 15 min after addition then allow to warm to room temperature. Monitor reaction progress by TLC. Reaction is usually complete in 3 hrs.

[1017] Chill solution with ice bath. Quench with 100 mls 10% K₂CO₃ while stirring rapidly. Stir 10 min. then transfer to sep funnel and allow separation. Remove aqueous layer. Extract organic layer once with 10% HCl, once H₂O, and once with saturated NaCl solution. Dry organic layer with MgSO₄, filter and rotovap to dryness. Crystallize product from ether. Obtain NMR and mass spec (m/z=460).

[1018] Step 8



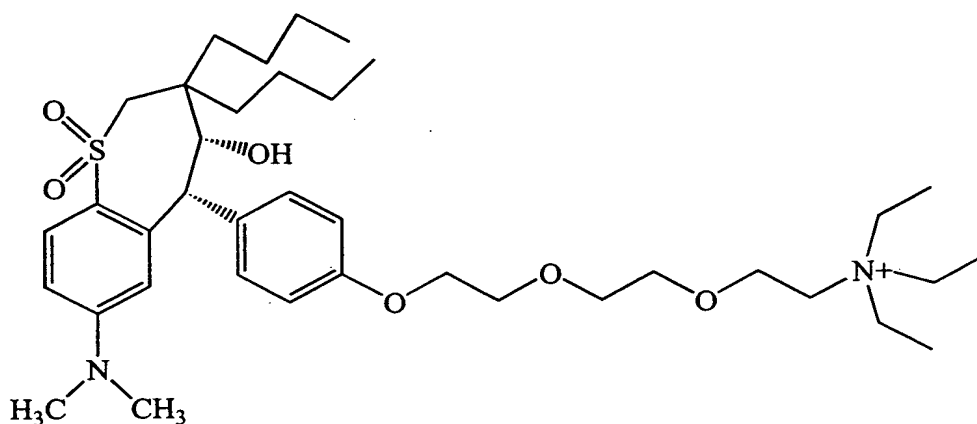
[1019] Weigh 0.38 gms NaH (9.57 mmoles Aldrich 19,923-0 60% disp. in mineral oil) in a 250 ml round bottom flask with magnetic stir bar. Fit flask with N₂ inlet and stopper. Chill NaH with ice bath and begin N₂ purge.

[1020] Dissolve 4.0 gms (8.7 mmoles) of product 7 with 60 mls anhydrous DMF. Add to the cold NaH. Stir at cold temperature for 30 min. Add 1.33 gms K₂CO₃ (9.57 mmoles Fisher P-208).

[1021] Dissolve 16.1 gms 1,2-bis-(2-iodoethoxy)ethane (43.5 mmoles Aldrich 33,343-3) with 60 mls anhydrous DMF. Add to cold reaction mixture. Warm to room temperature then heat to 40°C overnight under N₂.

[1022] Cleanup by diluting with ether and extracting sequentially with 5% NaOH, H₂O, and saturated NaCl. Dry organic layer with MgSO₄, filter and dry. Obtain pure product by column chromatography using 75% hexane 25% ethyl acetate as the mobile phase. Obtain NMR and mass spec (m/z=702).

[1023] Step 9

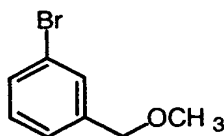


[1024] Dissolve 1.0 gms (1.43 mmoles) of product 8 with 10 mls anhydrous acetonitrile. Place in a 3 ounce Fischer-Porter pressure reaction vessel with magnetic stir bar. Add 2.9 gms triethyl amine (28.6 mmoles Aldrich 23,962-3) dissolved in 10 mls anhydrous acetonitrile. Purge well with N₂ then close system. Heat at 45°C. Monitor reaction by TLC. Reaction is usually complete in 48 hrs.

[1025] Perform cleanup by removing acetonitrile under vacuum. Redissolve with anhydrous chloroform and precipitate quaternary ammonium salt with ether. Repeat several times. Dry to obtain crystalline product. Obtain NMR and mass spec (m/z=675).

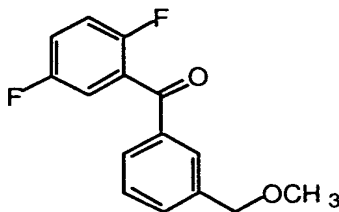
[1026] Example 1399

[1027] **Step 1. Preparation f 1**



[1028] To a solution of 144 g of KOH (2560 mmol) in 1.1 L of DMSO was added 120 g of 2-bromobenzyl alcohol (641 mmol) slowly via addition funnel. Then was added 182 g of methyl iodide (80 mL, 1282 mmol) via addition funnel. Stirred at ambient temperature for fifteen minutes. Poured reaction contents into 1.0 L of water and extracted three times with ethyl acetate. The organic layer was dried over MgSO_4 and concentrated in vacuo. Purified by silica-gel chromatography through a 200 mL plug using hexanes (100%) as elutant yielded 103.2 g (80%) of **1** as a clear colorless liquid. ^1H NMR (CDCl_3) δ 3.39 (s, 3H), 4.42 (s, 2H), 7.18-7.27 (m, 2H), 7.12 (d, $J = 7.45$, 1H), 7.50 (s, 1H).

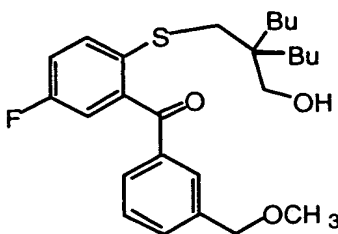
[1029] **Step 2. Preparation of 2**



[1030] To a cooled (-78°C) solution of 95 g (472 mmol) of **1** in 1.5 L THF was added 240 mL of 2.5 M *n*-butyl lithium (576 mmol). The mixture was stirred for one hour, and then to it was added 180 g of zinc iodide (566 mmol) dissolved in 500 mL THF. The mixture was stirred thirty minutes, allowed to warm to 5°C , cooled to -10°C and to it was added 6 g of $\text{Pd}(\text{PPh}_3)_4$ (5.2 mmol) and 125 g 2,5-difluorobenzoyl chloride (708 mmol). The mixture was stirred at ambient temperature for 18 hours and then cooled to 10°C , quenched with water, partitioned between ethyl acetate and water, and washed organic layer with 1N HCL and with 1N NaOH. The organic layer was dried over MgSO_4 and concentrated in vacuo. Purification by silica gel chromatography (Waters

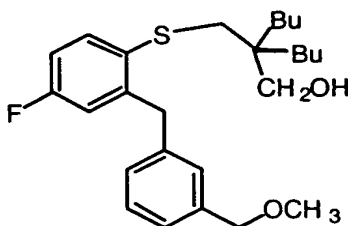
Prep-500) using 5% ethyl acetate/hexanes as elutant gave 53.6 g (43 %) of 2 as an orange oil. ^1H NMR (CDCl_3) δ 3.40 (s, 3H), 4.51 (s, 2H), 7.12-7.26 (m, 3H), 7.47 (t, $J = 7.50$; 1H), 7.57 (d, $J = 7.45$, 1H), 7.73 (d, $J = 7.45$, 1H), 7.80 (s, 1H).

[1031] Step 3. Preparation of 3



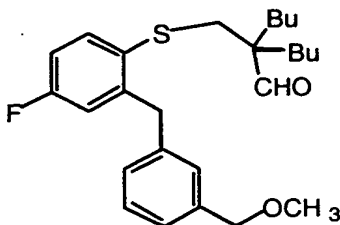
[1032] A solution of 53 g (202.3 mmol) of 2 and 11.2 g Li_2S (242.8 mmol) in 250 mL DMF was heated to 100°C for 18 hours. The reaction was cooled (0°C) and 60.7 g of X' (the cyclic sulfate compound of example 1397) (242.8 mmol) in 50 mL DMF was added. Stirred at ambient temperature for 18 hours then condensed in vacuo. Added 1 L water to organic residue and extracted twice with diethyl ether. Aqueous layer acidified (pH 1) and refluxed 2 days. Cooled to ambient temperature and extracted with methylene chloride, dried organic layer over MgSO_4 and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate / hexanes as elutant gave 42.9 g (48 %) of 3 as a yellow oil. ^1H NMR (CDCl_3) δ 0.86 (t, $J = 7.25$ Hz, 6H), 1.10 - 1.26 (m, 12H), 2.83 (s, 2H), 3.32 (s, 2H), 3.40 (s, 3H), 4.48 (s, 3H), 7.02 (dd, $J = 8.26$ Hz and 2.82 Hz, 1H), 7.16 (dt, $J = 8.19$ Hz and 2.82 Hz, 1H), 7.45 (t, $J = 7.65$ Hz, 1H), 7.56-7.61 (m, 2H), 7.69 (d, $J = 7.85$ Hz, 1H), 7.74 (s, 1H).

[1033] Step 4. Preparation of 4



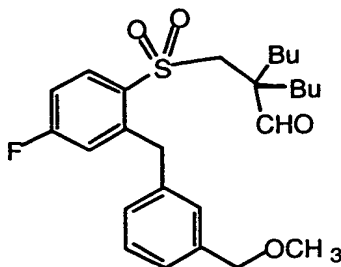
[1034] To a cooled (-40 °C) solution of 42.9 g (96.2 mmol) of 3 in 200 mL of methylene chloride was added 21.6 g trifluoromethane sulfonic acid (12.8 mL, 144 mmol) followed by the addition of 22.4 g triethyl silane (30.7 mL, 192.4 mmol). Stirred at -20°C for two hours, quenched with water and warmed to ambient temperature. Partitioned between methylene chloride and water, dried the organic layer over MgSO₄ and condensed in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 10% ethyl acetate/ hexanes as elutant gave 24.2 g (60%) of 4 as a oil. ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.05 Hz, 6H), 1.17 - 1.40 (m, 12H), 1.46 (t, J = 5.84 Hz, 1H), 2.81 (s, 2H), 3.38 (s, 3H), 3.43 (d, J = 5.23 Hz, 2H), 4.16 (s, 2H), 4.42 (s, 2H), 6.80 (d, J = 9.67 Hz, 1H), 6.90 (t, J = 8.46 Hz, 1H), 7.09 (d, J = 7.45 Hz, 1H), 7.15 - 7.21 (m, 2H), 7.25 - 7.32 (m, 2H), 7.42 (m, 1H).

[1035] Step 5. Preparation of 5



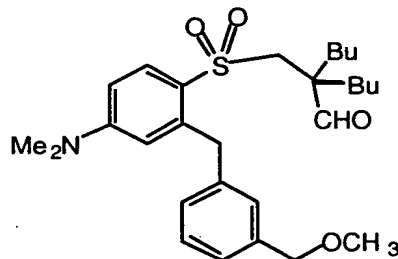
[1036] To a cooled (15-18 °C) solution of 24.2 g (55.8 mmol) of 4 in 100 mL DMSO was added 31.2 g sulfur trioxide pyridine complex (195 mmol). Stirred at ambient temperature for thirty minutes. Poured into cold water and extracted three times with ethyl acetate. Washed organics with 5% HCl (300 mL) and then with brine (300 mL), dried organics over MgSO₄ and condensed in vacuo to give 23.1 g (96 %) of 5 as a light brown oil. ¹H NMR (CDCl₃) δ 0.87 (t, J = 7.05 Hz, 6H), 1.01 - 1.32 (m, 8H), 1.53 - 1.65 (m, 4H), 2.98 (s, 2H), 3.38 (s, 3H), 4.15 (s, 2H), 4.43 (s, 2H), 6.81 (dd, J = 9.66 Hz and 2.82 Hz, 1H), 6.91 (t, J = 8.62 Hz, 1H), 7.07 (d, J = 7.46 Hz, 1H), 7.14 (s, 1H), 7.19 (d, J = 7.65 Hz, 1H), 7.26 - 7.32 (m, 1H), 7.42 (dd, J = 8.66 Hz and 5.64 Hz, 1H), 9.40 (s, 1H).

[1037] Step 6. Preparation of 6



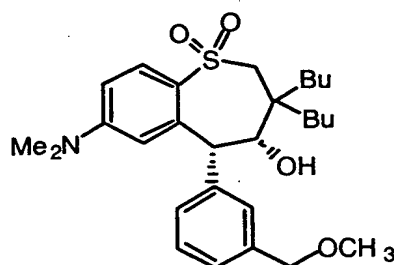
[1038] To a cooled (0 °C) solution of 23.1 g (53.6 mmol) of **5** in 200 mL methylene chloride was added 28.6 g meta chloroperoxy-benzoic acid (112.6 mmol). Stirred at ambient temperature for 24 hours. Quenched with 100 mL 10% Na₂SO₃, partitioned between water and methylene chloride. Dried organic layer over MgSO₄ and condensed in vacuo to give 24.5 g (98%) of **6** as a light yellow oil. ¹H NMR (CDCl₃) δ 0.86 - 1.29 (m, 14H), 1.58 - 1.63 (m, 2H), 1.82 - 1.91 (m, 2H), 3.13 (s, 2H), 3.39 (s, 3H), 4.44 (s, 2H), 4.50 (s, 2H), 6.93 (d, J = 9.07 Hz, 1H), 7.10 - 7.33 (m, 5H), 8.05 (s, 1H), 9.38 (s, 1H).

[1039] Step 7. Preparation of **7**



[1040] To a solution of 24.5 g (52.9 mmol) of **6** in 20 mL of THF contained in a stainless steel reaction vessel was added 100 mL of a 2.0 M solution of dimethyl amine and 20 mL of neat dimethyl amine. The vessel was sealed and heated to 110°C for 16 hours. The reaction vessel was cooled to ambient temperature and the contents concentrated in vacuo. Purification by silica gel chromatography (Waters Prep-500) using 15 % ethyl acetate/hexanes gave 21.8 g (84 %) of **7** as a clear colorless oil. ¹H NMR (CDCl₃) δ 0.85 (t, J = 7.25 Hz, 6H), 0.93 - 1.29 (m, 8H), 1.49 - 1.59 (m, 2H), 1.70 - 1.80 (m, 2H), 2.98 (s, 8H), 3.37 (s, 3H), 4.41 (s, 2H), 4.44 (s, 2H), 6.42 (s, 1H), 6.58 (dd, J = 9.0 Hz and 2.61 Hz, 1H), 7.13 (d, J = 7.45 Hz, 1H), 7.21 (s, 1H), 7.28 (t, J = 7.85 Hz, 1H), 7.82 (d, J = 9.06 Hz, 1H), 9.36 (s, 1H).

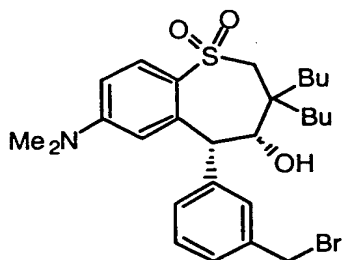
[1041] Step 8. Preparation of 7



[1042] A solution of 21.8 g (44.8 mmol) of **7** in 600 mL of THF was cooled to 0 °C. 58.2 mL of a 1 M solution of potassium

[1043] t-butoxide was added slowly, maintaining the temperature at <5 °C. Stirred for 30 minutes, then quenched with 50 mL of saturated ammonium chloride. The organic layer was partitioned between ethyl acetate and water, dried over MgSO₄ and concentrated in vacuo. Purification by recrystallization from ~10% ethyl acetate/hexanes gave 15.1 g of **8** as a white solid. The mother liquor was purified by silica gel chromatography (Waters Prep-500) using 30% ethyl acetate/hexanes as the elutant to give 3.0 g of **8** as a white solid. MS (FABLi⁺) m/e 494.6. HRMS (EI⁺) calculated for M+H 487.2756. Found 487.2746.

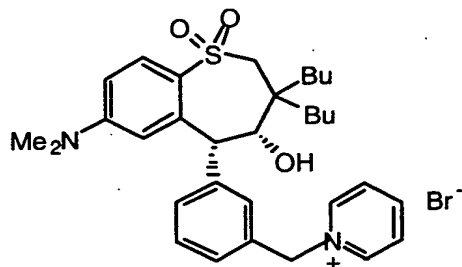
[1044] Step 9. Preparation of 9



[1045] A solution of 2.0 g (4.1 mmol) of **8** in 20 mL of methylene chloride was cooled to -60 °C. 4.1 mL of a 1M solution of boron tribromide was added. Stirred at ambient temperature for thirty minutes. Cooled reaction to ~10°C and quenched with 50 mL of water. The organic layer was partitioned between methylene chloride and water, dried over MgSO₄ and concentrated in vacuo. Purification by recrystallization from 50% ethyl acetate/methylene

chloride gave 1.95 g (89%) of **9** as a white solid. MS (FABH⁺) m/e 537. HRMS (FAB) calculated for M 536.1834. Found 536.1822.

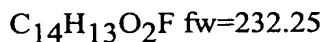
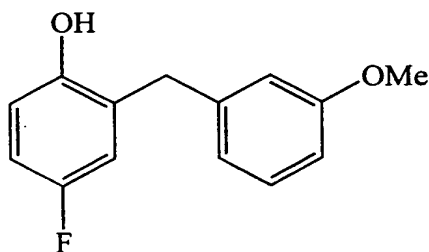
[1046] Step 10. Preparation of 10



[1047] A solution of 1.09 g (2.0 mmol) of **9** and 4.9 g (62 mmol) of pyridine in 30 mL of acetonitrile was stirred at ambient temperature for 18 hours. The reaction was concentrated in vacuo. Purification by recrystallization from methanol/ diethyl ether gave 1.19 g (96%) of **10** as an off white solid. MS (FAB⁺) m/e 535.5.

[1048] Example 1400

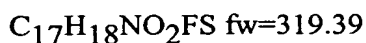
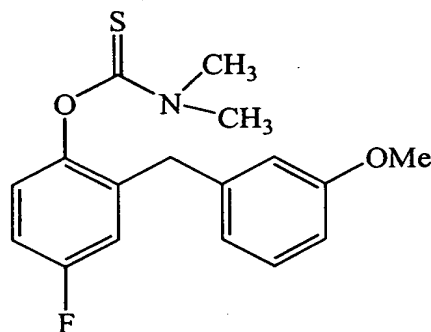
[1049] Step 1



[1050] A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N₂ gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N₂. A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6°C. A solution of 4-fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in

toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H₂O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aq. KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ¹H NMR and MS [(M + H)⁺ = 233] confirmed desired structure.

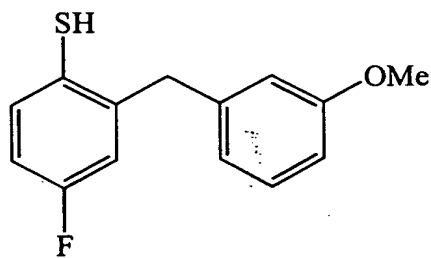
[1051] Step 2



[1052] A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N₂ gas adaptor. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature, dimethylthiocarbonyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H₂O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H₂O and

saturated aqueous NaCl, dried (MgSO₄), filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ¹H NMR and MS [(M+H)⁺ = 320] confirm desired structure.

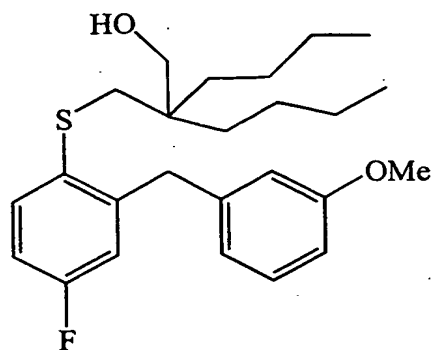
[1053] Step 3



C₁₄H₁₃OFS fw=248.32

[1054] A 12-liter, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temperature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H₂O. The aqueous extracts were combined, acidified with concentrated HCl, and extracted with ethyl ether. The ether extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ¹H NMR confirmed desired structure.

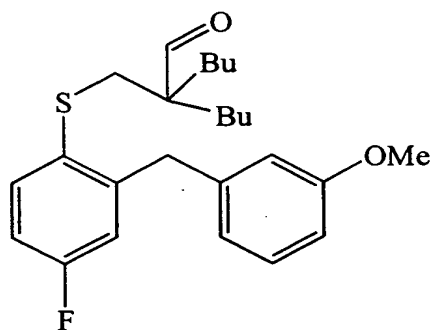
[1055] Step 4



$C_{25}H_{35}O_2FS$ fw=418.61

[1056] A 5-liter, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and mechanical stirrer. The system was purged with N_2 . 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to $0^\circ C$. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature, 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H_2O . The aqueous solution was washed with ethyl ether, and concentrated H_2SO_4 was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried ($MgSO_4$), filtered, and conc'd *in vacuo* to give an amber oil (143.94g/85% yield). 1H NMR and MS $[(M + H)^+ = 419]$ confirm the desired structure.

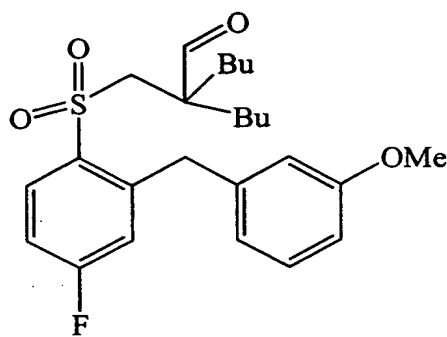
[1057] Step 5



$C_{25}H_{33}O_2FS$ fw=416.59

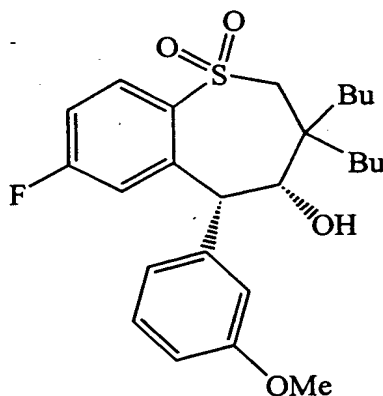
[1058] A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor, and mechanical stirrer. The system was purged with N₂. The corresponding alcohol (143.94g/343.8mmol) and CH₂Cl₂ (1.0 L) were added and cooled to 0°C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH₂Cl₂ was added. After 20 min, the mixture was filtered through silica gel, washing with CH₂Cl₂. The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ¹H NMR and MS [(M + H)⁺ = 417] confirm the desired structure.

[1059] Step 6



[1060] A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor and mechanical stirrer. The system was purged with N₂. The corresponding sulfide (110.6g/265.5mmol) and CH₂Cl₂ (1.0 L) were added. The solution was cooled to 0 C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature. After 3.5 h, the reaction mixture was cooled to 0°C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K₂CO₃. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried (MgSO₄), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ¹H NMR confirmed the desired structure.

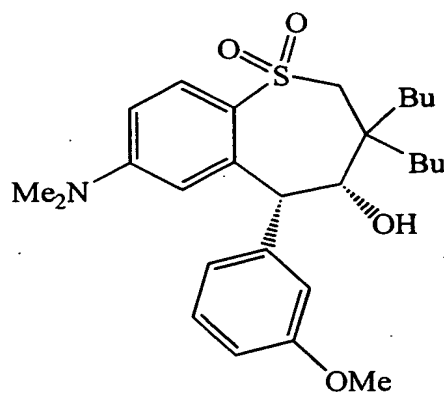
[1061] Step 7



$C_{25}H_{33}O_4FS$ fw=448.59

[1062] A 2-liter, 4-neck, round-bottom flask was equipped with N_2 gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N_2 . The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to $0^\circ C$. Potassium *tert*-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by recryst. from 80/20 hexane/ethyl acetate to give a white solid (32.18 g). The mother liquor was concentrated in vacuo and recrystelized from 95/5 toluene/ethyl acetate to give a white solid (33.60g/ combined yield: 71%). 1H NMR confirmed the desired product.

[1063] Step 8

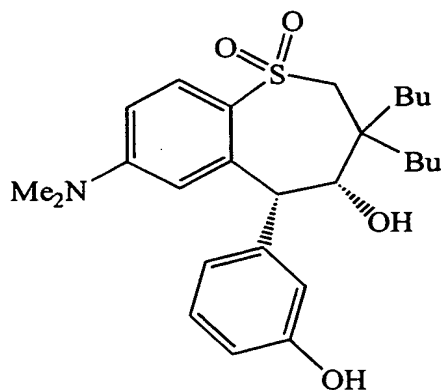


621



[1064] A Fisher porter bottle was fitted with N_2 line and magnetic stirrer. The system was purged with N_2 . The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78°C . Dimethylamine (17.1g/379mmol) was condensed via a CO_2 /acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60°C . After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H_2O , saturated aqueous NaCl , dried (MgSO_4), filtered, and concentrated *in vacuo* to give a white solid (28.5g/96% yield). ^1H NMR confirmed the desired structure.

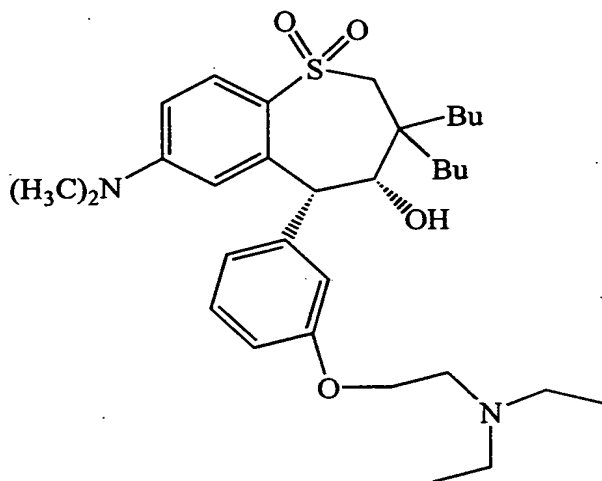
[1065] Step 9



[1066] A 250-mL, 3-neck, round-bottom flask was equipped with N_2 gas adaptor and magnetic stirrer. The system was purged with N_2 . The corresponding methoxy-compound (6.62g/14.0mmol) and CHCl_3 (150 mL) were added. The reaction mixture was cooled to -78°C , and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature. After 4 h, the reaction mixture was cooled to 0°C and was quenched with 10% K_2CO_3 (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether.

The CHCl_3 and ether extracts were combined, washed with saturated aqueous NaCl , dried (MgSO_4), filtered, and concentrated *in vacuo* to give the product (6.27g/98% yield). ^1H NMR confirmed the desired structure.

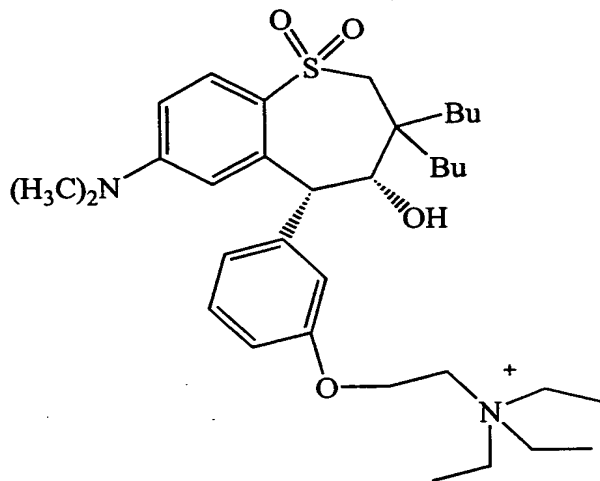
[1067] Step 10



[1068] In a 250 ml single neck round bottom Flask with stir bar place 2-diethylaminoethyl chloride hydrochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 mmol, 4.12g), 34 ml dry ether and 34 ml of 1N KOH(aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

[1069] In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg, 2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product(previous step) 1.1 g (2.4 mmol) in 5 ml DMF and the ether solution prepared above. Heat to 40°C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms). The product may be further purified by chromatography (SiO_2 99% ethyl acetate/1% NH_4OH at 5ml/min.). Isolated yield: 0.78 g (mass spec, and ^1H NMR)

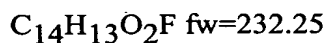
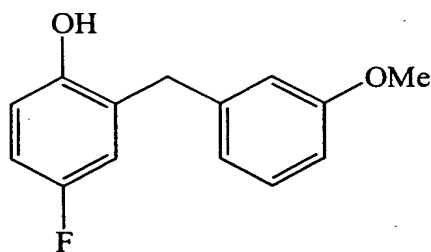
[1070] Step 11



[1071] The product from step 10 (0.57gms, 1.02 millimole fw 558.83 g/mole) and 1.6 gms iodoethane (10.02 mmol) was placed in 5 ml acetonitrile in a fischer-porter bottle and heated to 45°C for 3 days. The solution was evaporated to dryness and redissolved in 5 mls of chloroform. Next ether was added to the chloroform solution and the resulting mixture was chilled. The desired product is isolated as a precipitate 0.7272 gms. Mass spec M-I = 587.9 , H NMR).

[1072] Example 1401

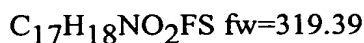
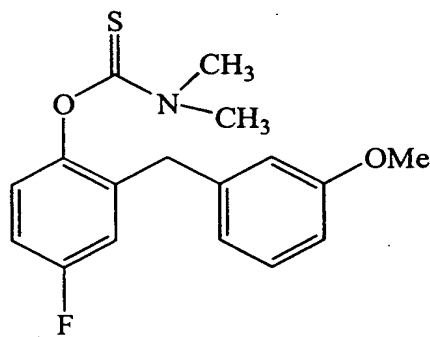
[1073] Step 1



[1074] A 12-liter, 4-neck round-bottom flask was equipped with reflux condenser, N_2 gas adaptor, mechanical stirrer, and an addition funnel. The system was purged with N_2 . A slurry of sodium hydride (126.0g/4.988mol) in toluene (2.5 L) was added, and the mixture was cooled to 6°C. A solution of 4-

fluorophenol (560.5g/5.000mol) in toluene (2.5 L) was added via addition funnel over a period of 2.5 h. The reaction mixture was heated to reflux (100 C) for 1h. A solution of 3-methoxybenzyl chloride (783.0g/5.000mol) in toluene (750 mL) was added via addition funnel while maintaining reflux. After 15 h. refluxing, the mixture was cooled to room temperature and poured into H₂O (2.5 L). After 20 min. stirring, the layers were separated, and the organic layer was extracted with a solution of potassium hydroxide (720g) in MeOH (2.5 L). The MeOH layer was added to 20% aqueous potassium hydroxide, and the mixture was stirred for 30 min. The mixture was then washed 5 times with toluene. The toluene washes were extracted with 20% aq. KOH. All 20% aqueous KOH solutions were combined and acidified with concentrated HCl. The acidic solution was extracted three times with ethyl ether, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by Kugelrohr distillation to give a clear, colorless oil (449.0g/39% yield). b.p.: 120-130 C/50mtorrHg. ¹H NMR and MS [(M + H)⁺ = 233] confirmed desired structure.

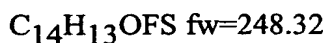
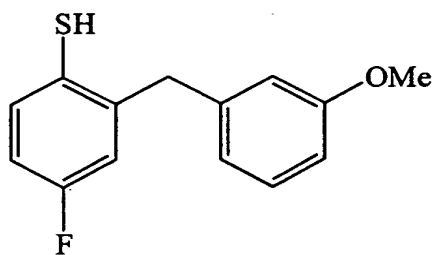
[1075] Step 2



[1076] A 12-liter, 3-neck round-bottom flask was fitted with mechanical stirrer and N₂ gas adaptor. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenol (455.5g/1.961mol) and dimethylformamide were added. The solution was cooled to 6 C, and sodium hydride (55.5g/2.197mol) was added slowly. After warming to room temperature,

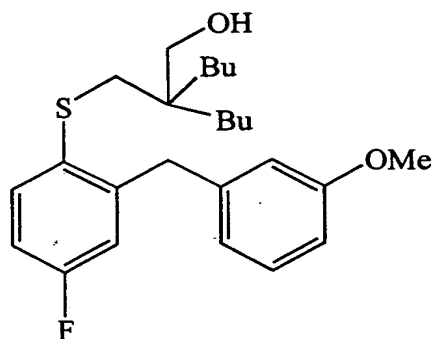
dimethylthiocarbamoyl chloride (242.4g/1.961mol) was added. After 15 h, the reaction mixture was poured into H₂O (4.0 L), and extracted two times with ethyl ether. The combined organic layers were washed with H₂O and saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated in vacuo to give the product (605.3g, 97% yield). ¹H NMR and MS [(M+H)⁺ = 320] confirm desired structure.

[1077] Step 3



[1078] A 12-liter, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and reflux condenser. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-phenyldimethylthiocarbamate (605.3g/1.895mol) and phenyl ether (2.0kg) were added, and the solution was heated to reflux for 2 h. The mixture was stirred for 64 h. at room temperature and then heated to reflux for 2 h. After cooling to room temperature, MeOH (2.0 L) and THF (2.0 L) were added, and the solution was stirred for 15 h. Potassium hydroxide (425.9g/7.590mol) was added, and the mixture was heated to reflux for 4 h. After cooling to room temperature, the mixture was concentrated by rotavap, dissolved in ethyl ether (1.0 L), and extracted with H₂O. The aqueous extracts were combined, acidified with conc. HCl, and extracted with ethyl ether. The ether extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* to give an amber oil (463.0g, 98% yield). ¹H NMR confirmed desired structure.

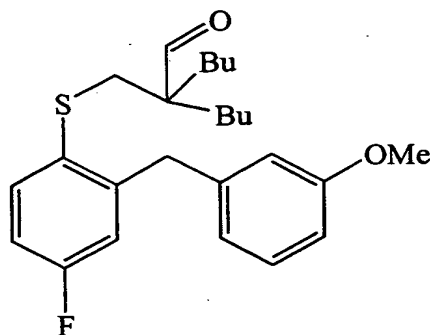
[1079] Step 4



C₂₅H₃₅O₂FS fw=418.61

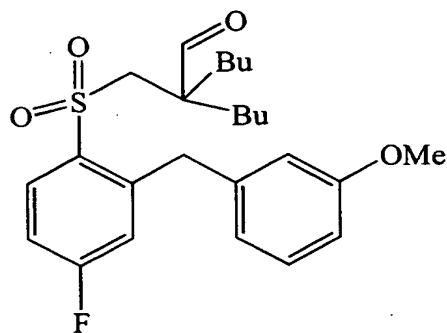
[1080] A 5-liter, 3-neck, round-bottom flask was equipped with N₂ gas adaptor and mechanical stirrer. The system was purged with N₂. 4-Fluoro-2-(3-methoxybenzyl)-thiophenol (100.0g/403.2mmol) and 2-methoxyethyl ether (1.0 L) were added and the solution was cooled to 0°C. Sodium hydride (9.68g/383.2mmol) was added slowly, and the mixture was allowed to warm to room temperature. 2,2-Dibutylpropylene sulfate (110.89g/443.6mmol) was added, and the mixture was stirred for 64 h. The reaction mixture was concentrated by rotavap and dissolved in H₂O. The aqueous solution was washed with ethyl ether, and conc. H₂SO₄ was added. The aqueous solution was heated to reflux for 30 min, cooled to room temperature, and extracted with ethyl ether. The ether solution was dried (MgSO₄), filtered, and concentrated *in vacuo* to give an amber oil (143.94g/85% yield). ¹H NMR and MS [(M + H)⁺ = 419] confirm the desired structure.

[1081] Step 5



[1082] A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor, and mechanical stirrer. The system was purged with N₂. The corresponding alcohol (143.94 g/343.8 mmol) and CH₂Cl₂ (1.0 L) were added and cooled to 0°C. Pyridinium chlorochromate (140.53g/651.6mmol) was added. After 6 h., CH₂Cl₂ was added. After 20 min, the mixture was filtered through silica gel, washing with CH₂Cl₂. The filtrate was concentrated *in vacuo* to give a dark yellow-red oil (110.6g, 77% yield). ¹H NMR and MS [(M + H)⁺ = 417] confirm the desired structure.

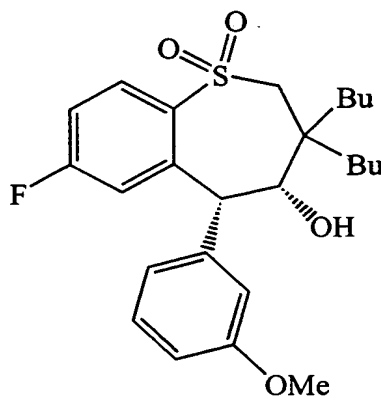
[1083] Step 6



[1084] A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor and mechanical stirrer. The system was purged with N₂. The corresponding sulfide (110.6g/265.5mmol) and CH₂Cl₂ (1.0 L) were added. The solution

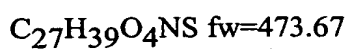
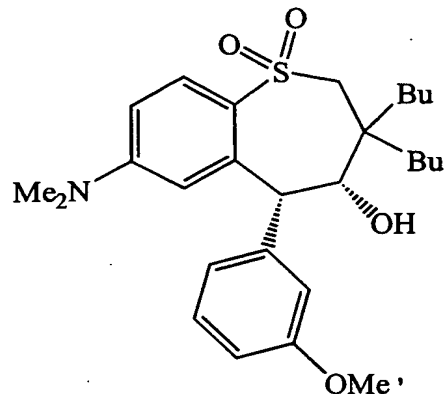
was cooled to 0 °C, and 3-chloroperbenzoic acid (158.21g/531.7mmol) was added portionwise. After 30 min, the reaction mixture was allowed to warm to room temperature. After 3.5 h, the reaction mixture was cooled to 0 °C and filtered through a fine fritted funnel. The filtrate was washed with 10% aqueous K₂CO₃. An emulsion formed which was extracted with ethyl ether. The organic layers were combined, dried (MgSO₄), filtered, and concentrated *in vacuo* to give the product (93.2g, 78% yield). ¹H NMR confirmed the desired structure.

[1085] Step 7



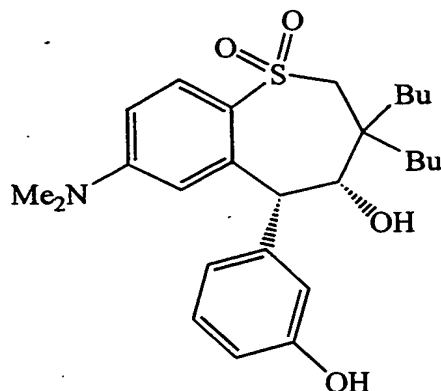
[1086] A 2-liter, 4-neck, round-bottom flask was equipped with N₂ gas adaptor, mechanical stirrer, and a powder addition funnel. The system was purged with N₂. The corresponding aldehyde (93.2g/208mmol) and THF (1.0 L) were added, and the mixture was cooled to 0 °C. Potassium *tert*-butoxide (23.35g/208.1mmol) was added via addition funnel. After 1h, 10% aq/ HCl (1.0 L) was added. After 1 h, the mixture was extracted three times with ethyl ether, dried (MgSO₄), filtered, and concentrated *in vacuo*. The crude product was purified by recrystallized from 80/20 hexane/ethyl acetate to give a white solid (32.18g). The mother liquor was concentrated in vacuo and recrystallized from 95/5 toluene/ethyl acetate to give a white solid (33.60g, combined yield: 71%). ¹H NMR confirmed the desired product.

[1087] Step 8



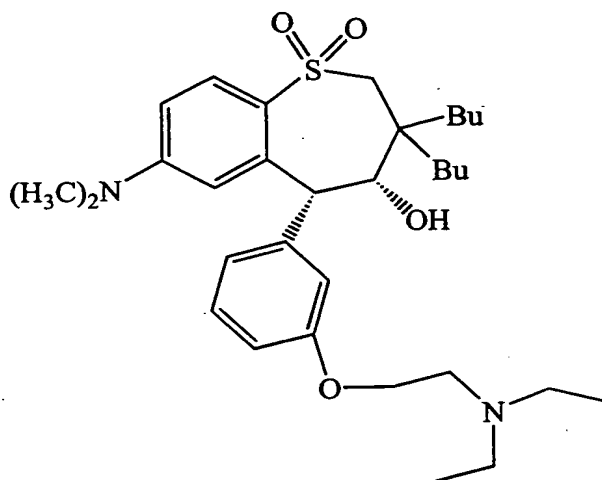
[1088] A Fisher porter bottle was fitted with N₂ line and magnetic stirrer. The system was purged with N₂. The corresponding fluoro-compound (28.1g/62.6mmol) was added, and the vessel was sealed and cooled to -78°C. Dimethylamine (17.1g/379mmol) was condensed via a CO₂/acetone bath and added to the reaction vessel. The mixture was allowed to warm to room temperature and was heated to 60°C. After 20 h, the reaction mixture was allowed to cool and was dissolved in ethyl ether. The ether solution was washed with H₂O, saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated *in vacuo* to give a white solid (28.5g/96% yield). ¹H NMR confirmed the desired structure.

[1089] Step 9



[1090] A 250-mL, 3-neck, round-bottom flask was equipped with N₂ gas adaptor and magnetic stirrer. The system was purged with N₂. The corresponding methoxy-compound (6.62g/14.0mmol) and CHCl₃ (150 mL) were added. The reaction mixture was cooled to -78 C, and boron tribromide (10.50g/41.9mmol) was added. The mixture was allowed to warm to room temperature. After 4 h, the reaction mixture was cooled to 0°C and was quenched with 10% K₂CO₃ (100 mL). After 10 min, the layers were separated, and the aqueous layer was extracted two times with ethyl ether. The CHCl₃ and ether extracts were combined, washed with saturated aqueous NaCl, dried over MgSO₄, filtered, and concentrated *in vacuo* to give the product (6.27g/98% yield). ¹H NMR confirmed the desired structure.

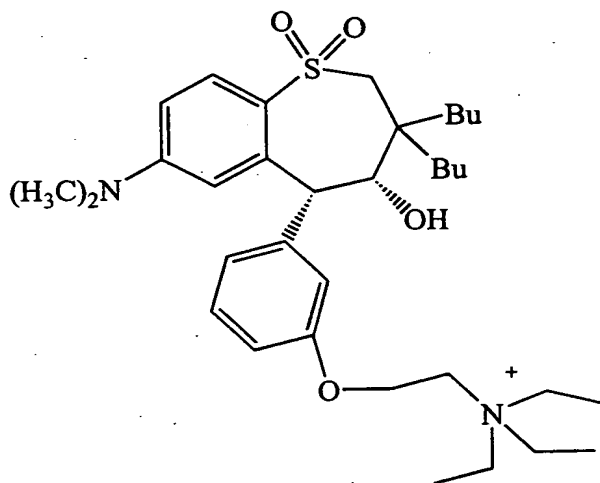
[1091] Step 10



[1092] In a 250 ml single neck round bottom flask with stir bar place 2-diethylaminoethyl chloride hydrochloride (fw 172.10g/mole) Aldrich D8, 720-1 (2.4 millimoles, 4.12g), 34 ml dry ether and 34 ml of 1N KOH (aqueous). Stir 15 minutes and then separate by ether extraction and dry over anhydrous potassium carbonate.

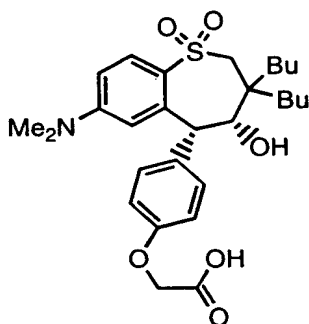
[1093] In a separate 2-necked 250 ml round bottom flask with stir bar add sodium hydride (60% dispersion in mineral oil, 100 mg, (2.6 mmol) and 34 ml of DMF. Cool to ice temperature. Next add phenol product (previous step) 1.1 g (2.4 mmol in 5 ml DMF and the ether solution prepared above. Heat to 40°C for 3 days. The product which contained no starting material by TLC was diluted with ether and extracted with 1 portion of 5% NaOH, followed by water and then brine. The ether layer was dried over Magnesium sulfate and isolated by removing ether by rotary evaporation (1.3 gms). The product may be further purified by chromatography (silica 99% ethyl acetate/1% NH₄OH at 5ml/min.). Isolated yield: 0.78 g (mass spec , and H1 NMR)

[1094] Step 11



[1095] The product from step 10 (0.57gms, 1.02 millimole fw 558.83 g/mole) and iodoethane (1.6 gms (10.02 mmilimoles) was placed in 5 ml acetonitrile in a Fischer-Porter bottle and heated to 45°C for 3 days. The solution was evaporated to dryness and redissolved in 5 mls of chloroform. Next ether was added to the chloroform solution and the resulting mixture was chilled. The desired product is isolated as a precipitate 0.7272 gms. Mass spec M-I = 587.9, ¹H NMR).

[1096] Example 1402



[1097] (4R-cis)-5-[[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]thio]-1H-tetrazole-1-acetic acid

[1098] Step 1. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol

[1099] To a stirred solution of 23.66 g of 95% sodium hydride (0.94 mol) in 600 mL of dry toluene was added 100.0 g of 4-fluorophenol (0.89 mol) at 0°C. The mixture was stirred at 90°C for 1 hour until gas evolution stopped. The mixture was cooled down to room temperature and a solution of 139.71 g of 3-methoxybenzyl chloride (0.89 mol) in 400 mL of dry toluene was added. After refluxing for 24 hours, the mixture was cooled to room temperature and quenched with 500 mL of water. The organic layer was separated, dried over MgSO₄, and concentrated under high vacuum. The remaining starting materials were removed by distillation. The crude dark red oil was filtered through a layer of 1 L of silica gel with neat hexane to yield 53.00 g (25.6%) of the product as a pink solid: ¹H NMR (CDCl₃) δ 3.79 (s, 3H), 3.90 (s, 2H), 4.58 (s, 1H), 6.70-6.74 (m, 1H), 6.79-6.88 (m, 4H), 7.11-7.16 (m, 2H).

[1100] Step 2. Preparation of 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

[1101] Step 2a. Preparation of thiocarbamate

[1102] To a stirred solution of 50.00 g (215.30 mmol) of 4-fluoro-2-((4-methoxyphenyl)methyl)-phenol in 500 mL of dry DMF was added 11.20 g of 60% sodium hydride dispersion in mineral oil (279.90 mmol) at 2°C. The mixture was allowed to warm to room temperature and 26.61 g of dimethylthiocarbamoyl chloride (215.30 mmol) was added. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with 100 mL of water in an ice bath. The solution was extracted with 500 mL of diethyl ether. The ether solution was washed with 500 mL of water and 500 mL of brine. The ether solution was dried over MgSO₄ and stripped to dryness. The crude product was filtered through a plug of 500 mL silica gel using 5% ethyl acetate/hexane to yield 48.00 g (69.8%) of the product as a pale white solid: ¹H NMR (CDCl₃) δ 3.21 (s, 3H), 3.46 (s, 3H), 3.80 (s, 3H), 3.82 (s, 2H), 6.78-6.86 (m, 3H), 6.90-7.00 (m, 2H), 7.09 (d, *J* = 8.7 Hz, 2H).

[1103] Step 2b. Rearrangement and hydrolysis of thiocarbamate to 4-fluoro-2-((4-methoxyphenyl)methyl)-thiophenol

[1104] A stirred solution of 48.00 g (150.29 mmol) of thiocarbamate (obtained from Step 2a) in 200 mL of diphenyl ether was refluxed at 270°C overnight. The solution was cooled down to room temperature and filtered through 1 L of silica gel with 2 L of hexane to remove phenyl ether. The rearrangement product was washed with 5% ethyl acetate/hexane to give 46.00 g (95.8%) of the product as a pale yellow solid: ^1H NMR (CDCl_3) δ 3.02 (s, 3H), 3.10 (s, 3H), 3.80 (s, 3H), 4.07 (s, 2H), 6.82-6.86 (m, 3H), 6.93 (dt, $J = 8.4$ Hz, 2.7 Hz, 1H), 7.08 (d, $J = 8.7$ Hz, 2H), 7.49 (dd, $J = 6.0$ Hz, 8.7 Hz, 1H).

[1105] To a solution of 46.00 g (144.02 mmol) of the rearrangement product (above) in 200 mL of methanol and 200 mL of THF was added 17.28 g of NaOH (432.06 mmol). The mixture was refluxed under nitrogen overnight. The solvents were evaporated off and 200 mL of water was added. The aqueous solution was washed with 200 mL of diethyl ether twice and placed in an ice bath. The aqueous mixture was acidified to pH 6 with concentrated HCl solution. The solution was extracted with 300 mL of diethyl ether twice. The ether layers were combined, dried over MgSO_4 and stripped to dryness to afford 27.00 g (75.5%) of the product as a brown oil: ^1H NMR (CDCl_3) δ 3.24 (s, 1H), 3.80 (s, 3H), 3.99 (s, 2H), 6.81-6.87 (m, 4H), 7.09 (d, $J = 8.7$ Hz, 2H), 7.27-7.33 (m, 1H).

[1106] **Step 3. Preparation of dibutyl cyclic sulfate**

[1107] **Step 3a. Preparation of 2,2-dibutyl-1,3-propanediol.**

[1108] To a stirred solution of di-butyl-diethylmalonate (Aldrich) (150g, 0.55 mol in dry THF (700ml) in an acetone/dry ice bath was added LAH (1 M THF) 662 ml (1.2 eq., 0.66 mol) dropwise maintaining the temperature between -20 to 0°C. The reaction was stirred at RT overnight. The reaction was cooled to -20°C and 40 ml of water, and 80 mL of 10% NaOH and 80 ml of water were added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulphate and concentrated *in vacuo* to give diol 98.4 g (yield 95%) as an oil. MS spectra and proton and carbon NMR spectra were consistent with the product.

[1109] Step 3b. Preparation of dibutyl cyclic sulfite

[1110] A solution of 2,2-dibutyl-1,3-propanediol (103 g, 0.548 mol, obtained from Step 3a) and triethylamine (221 g, 2.19 mol) in anhydrous methylene chloride (500 ml) was stirred at 0°C under nitrogen. To the mixture, thionyl chloride (97.8 g, 0.82 mol) was added dropwise and within 5 min the solution turned yellow and then black when the addition was completed within half an hour. The reaction mixture was stirred for 3 hrs. at 0°C. GC showed that there was no starting material left. The mixture was washed with ice water twice then with brine twice. The organic phase was dried over magnesium sulfate and concentrated under vacuum to give 128 g (100%) of the dibutyl cyclic sulfite as a black oil. Mass spectrum (MS) was consistent with the product.

[1111] Step 3c. Oxidation of dibutyl cyclic sulfite to dibutyl cyclic sulfate

[1112] To a solution of the dibutyl cyclic sulfite (127.5 g, 0.54 mol, obtained from Step 3b) in 600 ml acetonitrile and 500 ml of water cooled in an ice bath under nitrogen was added ruthenium (III) chloride (1 g) and sodium periodate (233 g, 1.08 mol). The reaction was stirred overnight and the color of the solution turned black. GC showed that there was no starting material left. The mixture was extracted with 300 ml of ether and the ether extract was washed three times with brine. The organic phase was dried over magnesium sulfate and passed through celite. The filtrate was concentrated under vacuum and to give 133 g (97.8%) of the dibutyl cyclic sulfate as an oil. Proton and carbon NMR and MS were consistent with the product.

[1113] Step 4. Preparation of aryl-3-hydroxypropylsulfide

[1114] To a stirred solution of 27.00 g (108.73 mmol) of 4-fluoro-2-((4-methoxyphenyl)methyl)thiophenol (obtained from Step 2) in 270 mL of diglyme was added 4.35 g of 60% sodium hydride dispersion in mineral oil (108.73 mmol) at 0°C. After gas evolution ceased, 29.94 g (119.60 mmol) of the dibutyl cyclic sulfate (obtained from Step 3c) was added at 0°C and stirred for 10 minutes. The mixture was allowed to warm up to room temperature and stirred overnight. The solvent was evaporated and 200 mL of water was

added. The solution was washed with 200 mL of diethyl ether and added 25 mL of concentrated sulfuric acid to make a 2.0 M solution that was refluxed overnight. The solution was extracted with ethyl acetate and the organic solution was dried over MgSO_4 and concentrated in vacuo. The crude aryl-3-hydroxypropylsulfide was purified by silica gel chromatography (Waters Prep 500) using 8% ethyl acetate/hexane to yield 33.00 g (72.5%) of the product as a light brown oil: ^1H NMR (CDCl_3) δ 0.90 (t, J = 7.1 Hz, 6H), 1.14-1.34 (m, 12H), 2.82 (s, 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10 (s, 2H), 6.77-6.92 (m, 4H), 7.09 (d, J = 8.7 Hz, 2H), 7.41 (dd, J = 8.7 Hz, 5.7 Hz, 1H).

[1115] Step 5. Preparation of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide

[1116] To a stirred solution of 20.00 g (47.78 mmol) of aryl-3-hydroxypropylsulfide (obtained from Step 4) in 1 L of methylene chloride was added 31.50 g of 96% (1*R*)-(-)-(8,8-dichloro-10-camphor-sulfonyl)oxaziridine (100.34 mmol, Aldrich) at 2°C. After all the oxaziridine dissolved the mixture was placed into a -30°C freezer for 72 hours. The solvent was evaporated and the crude solid was washed with 1 L of hexane. The white solid was filtered off and the hexane solution was concentrated in vacuo. The crude oil was purified on a silica gel column (Waters Prep 500) using 15% ethyl acetate/hexane to afford 19.00 g (95%) of the enantiomerically-enriched aryl-3-hydroxypropylsulfoxide as a colorless oil: ^1H NMR (CDCl_3) δ 0.82-0.98 (m, 6H), 1.16-1.32 (m, 12H), 2.29 (d, J = 13.8 Hz, 1H), 2.77 (d, J = 13.5 Hz, 1H), 3.45 (d, J = 12.3 Hz, 1H), 3.69 (d, J = 12.3 Hz, 1H), 3.79 (s, 3H), 4.02 (q, J = 15.6 Hz, 1H), 6.83-6.93 (m, 3H), 7.00 (d, J = 8.1 Hz, 2H), 7.18-7.23 (m, 1H), 7.99-8.04 (m, 1H). Enantiomeric excess was determined by chiral HPLC on a (*R,R*)-Whelk-O column using 5% ethanol/hexane as the eluent. It showed to be 78% e.e. with the first eluting peak as the major product.

[1117] Step 6. Preparation of enantiomerically-enriched aryl-3-propanalsulfoxide

[1118] To a stirred solution of 13.27 g of triethylamine (131.16 mmol, Aldrich) in 200 mL dimethyl sulfoxide were added 19.00 g (43.72 mmol) of enantiomerically-enriched aryl-3-hydroxypropylsulfoxide (obtained from Step 5) and 20.96 g of sulfur trioxide-pyridine (131.16 mmol, Aldrich) at room temperature. After the mixture was stirred at room temperature for 48 hours, 500 mL of water was added to the mixture and stirred vigorously. The mixture was then extracted with 500 mL of ethyl acetate twice. The ethyl acetate layer was separated, dried over MgSO_4 , and concentrated in vacuo. The crude oil was filtered through 500 mL of silica gel using 15% ethyl acetate/hexane to give 17.30 g (91%) of the enantiomerically-enriched aryl-3-propanalsulfoxide as a light orange oil: ^1H NMR (CDCl_3) δ 0.85-0.95 (m, 6H), 1.11-1.17 (m, 4H), 1.21-1.39 (m, 4H), 1.59-1.76 (m, 4H), 1.89-1.99 (m, 1H), 2.57 (d, J = 14.1 Hz, 1H), 2.91 (d, J = 13.8 Hz, 1H), 3.79 (s, 3H), 3.97 (d, J = 15.9 Hz, 1H), 4.12 (d, J = 15.9 Hz, 1H), 6.84-6.89 (m, 3H), 7.03 (d, J = 8.4 Hz, 2H), 7.19 (dt, J = 8.4 Hz, 2.4 Hz, 1H), 8.02 (dd, J = 8.7 Hz, 5.7 Hz, 1H), 9.49 (s, 1H).

[1119] Step 7. Preparation of the enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R,5R)

[1120] To a stirred solution of 17.30 g (39.99 mmol) of enantiomerically-enriched aryl-3-propanalsulfoxide (obtained from Step 6) in 300 mL of dry THF at -15°C was added 48 mL of 1.0 M potassium *t*-butoxide in THF (1.2 equivalents) under nitrogen. The solution was stirred at -15°C for 4 hours. The solution was then quenched with 100 mL of water and neutralized with 4 mL of concentrated HCl solution at 0°C . The THF layer was separated, dried over MgSO_4 , and concentrated in vacuo. The enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (4R,5R) was purified by silica gel chromatography (Waters Prep 500) using 15% ethyl acetate/hexane to give 13.44 g (77.7%) of the product as a white solid: ^1H NMR (CDCl_3) δ 0.87-0.97 (m, 6H), 1.16-1.32 (m, 4H), 1.34-1.48 (m, 4H), 1.50-1.69 (m, 4H), 1.86-1.96 (m, 1H), 2.88 (d, J = 13.0 Hz, 1H), 3.00 (d, J = 13.0 Hz, 1H), 3.85 (s, 3H), 4.00 (s, 1H), 4.48 (s, 1H), 6.52 (dd, J = 9.9 Hz, 2.4 Hz, 1H), 6.94 (d, J = 9 Hz,

2H), 7.13 (dt, $J = 8.4$ Hz, 2.4 Hz, 1H), 7.38 (d, $J = 8.7$ Hz, 2H), 7.82 (dd, $J = 8.7$ Hz, 5.7 Hz, 1H).

[1121] Step 8. Preparation of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

[1122] To a stirred solution of 13.44 g (31.07 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1-oxide (obtained from Step 7) in 150 mL of methylene chloride was added 9.46 g of 68% *m*-chloroperoxybenzoic acid (37.28 mmol, Sigma) at 0 °C. After stirring at 0 °C for 2 hours, the mixture was allowed to warm up to room temperature and stirred for 4 hours. 50 mL of saturated Na₂SO₃ was added into the mixture and stirred for 30 minutes. The solution was then neutralized with 50 mL of saturated NaHCO₃ solution. The methylene chloride layer was separated, dried over MgSO₄, and concentrated in vacuo to give 13.00 g (97.5%) of the enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (4R,5R) as a light yellow solid: ¹H NMR (CDCl₃) δ 0.89-0.95 (m, 6H), 1.09-1.42 (m, 12H), 2.16-2.26 (m, 1H), 3.14 (q, $J = 15.6$ Hz, 1H), 3.87 (s, 3H), 4.18 (s, 1H), 5.48 (s, 1H), 6.54 (dd, $J = 10.2$ Hz, 2.4 Hz, 1H), 6.96-7.07 (m, 3H), 7.40 (d, $J = 8.1$ Hz, 2H), 8.11 (dd, $J = 8.6$ Hz, 5.9 Hz, 1H).

[1123] Step 9. Preparation of enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

[1124] To a solution of 13.00 g (28.98 mmol) of enantiomerically-enriched tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 8) in 73 mL of dimethylamine (2.0 M in THF, 146 mmol) in a Parr Reactor was added about 20 mL of neat dimethylamine. The mixture was sealed and stirred at 110°C overnight, and cooled to ambient temperature. The excess dimethylamine was evaporated. The crude oil was dissolved in 200 mL of ethyl acetate and washed with 100 mL of water, dried over MgSO₄ and concentrated in vacuo. Purification on a silica gel column (Waters Prep 500) using 20% ethyl acetate/hexane gave 12.43 g (90.5%) of the enantiomerically-enriched 7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R) as a colorless

solid: ^1H NMR (CDCl_3) δ 0.87-0.93 (m, 6H), 1.10-1.68 (m, 12H), 2.17-2.25 (m, 1H), 2.81 (s, 6H), 2.99 (d, $J = 15.3$ Hz, 1H), 3.15 (d, $J = 15.3$ Hz, 1H), 3.84 (s, 3H), 4.11 (d, $J = 7.5$ Hz, 1H), 5.49 (s, 1H), 5.99 (d, $J = 2.4$ Hz, 1H), 6.51 (dd, $J = 8.7$ Hz, 2.4 Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 8.7$ Hz, 1H). The product was determined to have 78% e.e. by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. Recrystallization of this solid from ethyl acetate/hexane gave 1.70 g of the racemic product. The remaining solution was concentrated and recrystallized to give 9.8 g of colorless solid. Enantiomeric excess of this solid was determined by chiral HPLC on a Chiralpak AD column using 5% ethanol/hexane as the eluent. It showed to have 96% e.e with the first eluting peak as the major product.

[1125] Step 10: Demethylation of 5-(4'-methoxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (4R,5R)

[1126] To a solution of 47 g (99 mmol) of enantiomeric-enriched (dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Step 9) in 500 mL of methylene chloride at -10°C was added dropwise a solution of boron tribromide (297 mL, 1M in methylene chloride, 297 mmol), and the resulting solution was stirred cold (-5°C to 0°C) for 1 hour or until the reaction was complete. The reaction was cooled in an acetone-dry ice bath at -10°C , and slowly quenched with 300 mL of water. The mixture was warmed to 10°C , and further diluted with 300 mL of saturated sodium bicarbonate solution to neutralize the mixture. The aqueous layer was separated and extracted with 300 mL of methylene chloride, and the combined extracts were washed with 200 mL of water, brine, dried over MgSO_4 and concentrated in vacuo. The residue was dissolved in 500 mL of ethyl acetate and stirred with 50 mL of glacial acetic acid for 30 minutes at ambient temperature. The mixture was washed twice with 200 mL of water, 200 mL of brine, dried over MgSO_4 and concentrated in vacuo to give the crude 4-hydroxyphenyl intermediate. The solid residue was recrystallized from methylene chloride to give 37.5 g (82%) of the desired 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide as a white solid: ^1H

NMR (CDCl₃) δ 0.84-0.97 (m, 6H), 1.1-1.5 (m, 10H), 1.57-1.72 (m, 1H), 2.14-2.28 (m, 1H), 2.83 (s, 6H), 3.00 (d, J = 15.3 Hz, 1H), 3.16 (d, J = 15.3 Hz, 1H), 4.11 (s, 2H), 5.48 (s, 1H), 6.02 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 9, 2.4 Hz, 1H), 6.88 (d, 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 9 Hz, 2H).

[1127] Alternatively, enantiomeric-enriched 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide, the intermediate just described, can be prepared via non-enantioselective synthesis followed by chiral chromatography separation. Oxidation of aryl-3-hydroxypropylsulfide (obtained from Step 4) with *m*-chloroperbenzoic acid (under the similar conditions as in Step 8, but with 2.2 equivalent of *m*-CPBA) gave the racemic sulfone intermediate. The sulfone was carried through the synthetic sequences (under the same conditions as in Step 7 and Step 9) to give the racemic 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide. The two enantiomers were further separated into the desired enantiomeric-enriched 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide by appropriate chiral chromatographic purification.

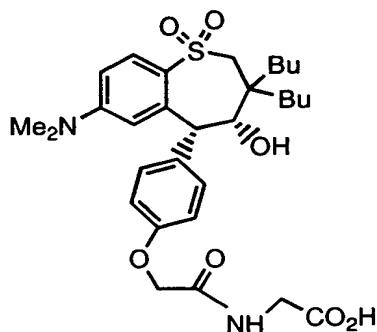
[1128] Step 11: Preparation of ester intermediate

[1129] To a solution of 1.0 g (2.18 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Step 10) in 10 mL dimethylformamide was added 60 mg (2.38 mmol) of 95% sodium hydride and stirred for 15 minutes. To the reaction mixture was added 400 μ L (2.52 mmol) of benzyl 2-bromoacetate and stirred for two hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 1.30g (98%) of the ester intermediate: ¹H NMR (CDCl₃) δ 0.88-0.94 (m, 6H), 1.13-1.46 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.24 (m, 1H), 2.81 (s, 6H), 3.00 (d, J = 15.1 Hz, 1H), 3.16 (t, J = 15.1 Hz, 1H), 4.11 (s, 1H), 5.26 (s, 2H), 5.49 (s, 1H), 6.04 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.9, 2.4 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 7.37 (s, 5H), 7.42 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.9 Hz, 1H).

[1130] Step 12: Preparation of acid

[1131] A solution of 1.30 g (2.14 mmol) of ester intermediate (obtained from Step 1) in 40 mL ethanol with 10% palladium on carbon was placed under an atmosphere of hydrogen gas (40 psi) for three hours. The reaction mixture was filtered through celite and the solvent was evaporated to afford the desired title compound as a white solid: mp 119 - 123 °C; ¹H NMR (CDCl₃) δ 0.89-0.94 (m, 6H), 1.19-1.43 (m, 10H), 1.61-1.65 (m, 1H), 2.17-2.21 (m, 1H), 2.85 (s, 6H), 3.02 (d, *J* = 15.1 Hz, 1H), 3.17 (t, *J* = 14.9 Hz, 1H), 4.12 (s, 1H), 4.72 (s, 2H), 5.51 (s, 1H), 6.17 (s, 1H), 6.74 (d, *J* = 9.1 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.7 Hz, 1H). HRMS. Calc'd for C₂₈H₄₀NO₆S: 518.2576. Found: 518.2599.

[1132] Example 1403



[1133] (4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxyacetyl]glycine

[1134] Step 1: Preparation of glycine ester intermediate

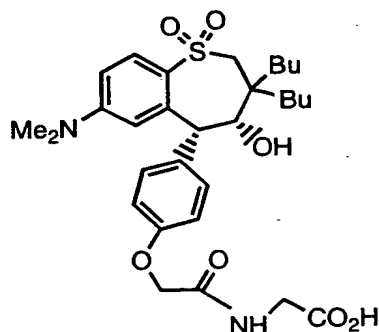
[1135] To a solution of 6.4 g (13.9 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 ml of acetone was added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction was heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours, then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO₄, and concentrated *in vacuo*.

Purification by silica gel chromatography (Waters Prep-500) using 50% ethyl acetate/hexanes afforded 7.5 g (90%) of glycine ester intermediate as a white foam: ^1H NMR (CDCl_3) δ 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q , $J_{\text{AB}} = 15.3$ Hz, $J = 48.9$ Hz, 2H), 4.06-4.19 (m, 6H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, $J = 8.6$ Hz, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 7.17 (s, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H).

[1136] Step 2: Preparation of acid

[1137] A solution of 7.3 g (12.1 mmol) of glycine ester intermediate (obtained from Step 1) and 1.5 g $\text{LiOH}\cdot\text{H}_2\text{O}$ (36.3 mmol) in 60 mL of THF and 60 mL of water was heated to 45°C for 2 hours. This was then cooled to ambient temperature, acidified with 1 N HCl and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. Purification by recrystallization from ethyl acetate gave 5.45 g (78%) of the desired title compound as a white crystalline solid: mp $149\text{--}150^\circ\text{C}$; ^1H NMR (CD_3OD) δ 0.88-0.98 (m, 6H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20 (m, 1H), 2.79 (s, 6H), 3.11 (AB_q , $J_{\text{AB}} = 15.3$ Hz, $J = 21.6$ Hz, 2H), 4.01 (s, 2H), 4.07 (s, 1H), 4.61 (s, 2H), 5.31 (s, 1H), 6.04 (s, 1H), 6.57 (d, $J = 9.0$ Hz, 1H), 7.08 (d, $J = 7.8$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 2H), 7.76 (d, $J = 9.0$ Hz, 1H), 8.42 (m, 1H). HRMS(ES+) Calc'd for $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_7\text{S}$: 575.2712. Found: 575.2790. Anal. Calc'd for: $\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_7\text{S}$ C, 62.69; H, 7.37; N, 4.87. Found: C, 62.87; H, 7.56; N, 4.87.

[1138] Example 1403



[1139] (4R-cis)-N-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxyacetyl]glycine

[1140] Step 1: Preparation of glycine ester intermediate

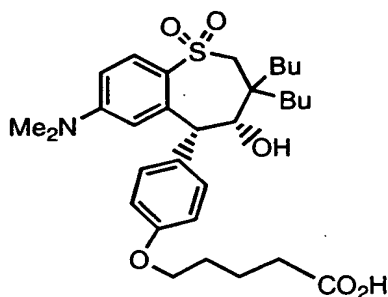
[1141] To a solution of 6.4 g (13.9 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 2.9 g (21.0 mmol) of potassium carbonate in 100 ml of acetone was added 3.8 g (21.0 mmol) of N-(chloroacetyl)glycine ethyl ester and 50 mg (0.14 mmol) of tetrabutylammonium iodide. The reaction was heated to reflux for 2 days, cooled to ambient temperature and stirred for 20 hours, then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. Purification by silica gel chromatography (Waters Prep-500) using 50% ethyl acetate/hexanes afforded 7.5 g (90%) of glycine ester intermediate as a white foam: ^1H NMR (CDCl_3) δ 0.86-0.98 (m, 6H), 1.04-1.56 (m, 13H), 1.58-1.71 (m, 1H), 2.14-2.29 (m, 1H), 2.73 (s, 6H), 3.08 (AB_q , $J_{\text{AB}} = 15.3$ Hz, $J = 48.9$ Hz, 2H), 4.06-4.19 (m, 6H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.57 (s, 2H), 5.50 (s, 1H), 5.98 (s, 1H), 6.56 (d, $J = 8.6$ Hz, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 7.17 (s, 1H), 7.47 (d, $J = 8.3$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H).

[1142] Step 2: Preparation of acid

[1143] A solution of 7.3 g (12.1 mmol) of glycine ester intermediate (obtained from Step 1) and 1.5 g $\text{LiOH}\cdot\text{H}_2\text{O}$ (36.3 mmol) in 60 mL of THF and 60 mL of water was heated to 45 °C for 2 hours. This was then cooled to ambient

temperature, acidified with 1 N HCl and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. Purification by recrystallization from ethyl acetate gave 5.45 g (78%) of the desired title compound as a white crystalline solid: mp 149-150 °C; ¹H NMR (CD₃OD) δ 0.88-0.98 (m, 6H), 1.06-1.56 (m, 10H), 1.70-1.84 (m, 1H), 2.06-2.20 (m, 1H), 2.79 (s, 6H), 3.11 (AB_q, *J*_{AB} = 15.3 Hz, *J* = 21.6 Hz, 2H), 4.01 (s, 2H), 4.07 (s, 1H), 4.61 (s, 2H), 5.31 (s, 1H), 6.04 (s, 1H), 6.57 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 1H), 8.42 (m, 1H). HRMS(ES⁺) Calc'd for C₃₀H₄₂N₂O₇S: 575.2712. Found: 575.2790. Anal. Calc'd for: C₃₀H₄₂N₂O₇S C, 62.69; H, 7.37; N, 4.87. Found: C, 62.87; H, 7.56; N, 4.87.

[1144] Example 1404



[1145] (4R-cis)-5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentanoic acid

[1146] **Step 1: Preparation of ester intermediate**

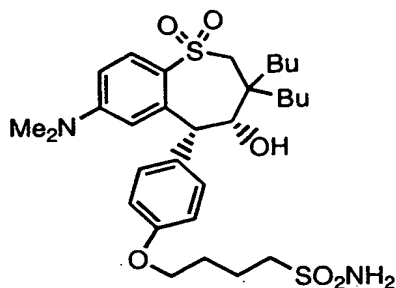
[1147] A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.0 g, 2.2 mmol, obtained from Example 1402, Step 10) in acetone (10 mL) at 25°C under N₂ was treated with powdered K₂CO₃ (0.45 g, 3.3 mmol, 1.5 eq.), benzyl 5-bromovalerate (0.88 g, 3.3 mmol, 1.5 eq.) and a catalytic amount of tetra-*n*-butylammonium iodide (2 mg), and the resulting solution was stirred at 65°C for 24 hours. The pale amber slurry was cooled to 25°C and was concentrated in vacuo to provide a yellow residue. Purification by flash chromatography (2.4 x 30 cm silica, 20-40% EtOAc/hexane) afforded the ester intermediate

(1.2 g, 86%) as a colorless oil: ^1H NMR (CDCl_3) δ 0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.64 (m, 1H), 1.86 (m, 2H), 2.21 (m, 1H), 2.47 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, $J = 15.1$ Hz, $J = 47.7$ Hz, 2H), 4.10 (d, $J = 7.9$ Hz, 1H), 5.13 (s, 2H), 5.47 (s, 1H), 6.00 (d, $J = 2.5$ Hz, 1H), 6.50 (dd, $J = 8.9$, 2.5 Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.36 (m, 5H), 7.40 (d, $J = 8.5$ Hz, 2H), 7.86 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $\text{C}_{38}\text{H}_{51}\text{NO}_6\text{S}$: 650.3515. Found: 650.3473.

[1148] Step 2: Preparation of acid

[1149] A solution of the ester intermediate (0.99 g, 1.5 mmol, obtained from Step 1) in ethanol (7.5 mL) at 25°C was treated with 5% palladium on carbon (0.15 g, 10 wt %) then stirred under an atmosphere (1 atm) of H_2 via hydrogen balloon. Every 10 min, hydrogen gas was bubbled through the slurry for 1 min, for a total reaction time of 4 hours. The slurry was placed under an atmosphere of N_2 and nitrogen was bubbled through the reaction mixture for 10 min. The mixture was filtered through a plug of Celite[®] (10 g) and concentrated in vacuo to give a white foam. Purification by flash chromatography (2.6 x 25 cm silica, 1.5% EtOH/ CH_2Cl_2) afforded the desired title compound (0.54 g, 63%) as a white foam: mp: 76-79 °C; ^1H NMR (CDCl_3) δ 0.90 (m, 6H), 1.10-1.46 (br m, 10H), 1.62 (m, 1H), 1.87 (m, 4H), 2.20 (m, 1H), 2.45 (m, 2H), 2.81 (s, 6H), 3.05 (ABq, $J = 15.1$ Hz, $J = 49.7$ Hz, 2H), 4.00 (s, 2H), 4.09 (s, 1H), 5.45 (s, 1H), 5.99 (d, $J = 2.4$ Hz, 1H), 6.48 (dd, $J = 8.9$, 2.4 Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.39 (m, 5H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.84 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $\text{C}_{31}\text{H}_{45}\text{NO}_6\text{S}$: 560.3046. Found: 560.3043.

[1150] Example 1405



[1151] (4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy-1-butanesulfonamide

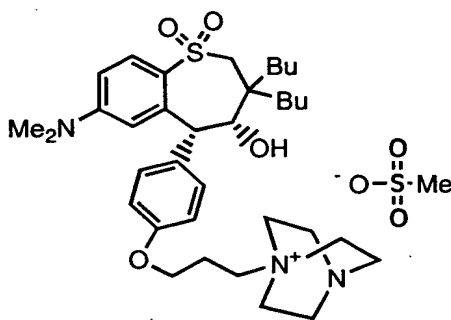
[1152] **Step 1: Preparation of sulfonic acid intermediate**

[1153] A solution of 7.4 g (16.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Example 1402, Step 10) in acetone (35 mL) at 25°C under N₂ was treated with powdered potassium carbonate (3.3 g, 24.1 mmol, 1.5 equiv.) and 1,4-butane sultone (2.5 mL, 24.1 mmol, 1.5 equiv.) and stirred and heated at 65°C for 64 h. The solution was allowed to cool to 25°C and quenched by the addition of water (50 mL), until a homogeneous mixture was obtained. The clear and colorless solution was added dropwise to a 4 N HCl solution cooled to 0°C over a 30 min period. The mixture was vigorously stirred for 4 h then allowed to warm to ambient temperature and stirred for an additional 16 h. The resultant white precipitate was filtered and washed with water and dried in vacuo to provide 8.8 g (92%) of the desired sulfonic acid as a white solid. A portion of the white solid was recrystallized from CH₃CN/hexane to give the desired sulfonic acid as colorless needles: mp 229-236°C (decomposed); ¹H NMR (DMSO-d₆) δ 0.82 (m, 6H), 1.02-1.33 (br m, 10H), 1.59 (m, 1H), 1.73 (m, 4H), 2.00 (s, 1H), 2.48 (m, 2H), 2.71 (s, 6H), 2.98 (s, 1H), 3.86 (s, 1H), 3.93 (m, 2H), 5.08 (s, 1H), 5.89 (s, 1H), 6.52 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.9 Hz, 1H); Anal. Calc'd for C₃₀H₄₅NO₇S₂: C, 60.48; H, 7.61; N, 2.35. Found: C, 60.53; H, 7.70; N, 2.42.

[1154] Step 2: Preparation of 7-(dimethylamin)-benz thiepin-5-yl]phenoxy-1-butanesulf namide

[1155] To a solution of 1.12 g (1.88 mmol) of the sulfonic acid (obtained from Step 1) in 10 mL CH₂Cl₂ was added 785 mg (3.77 mmol) PCl₅ and stirred for 1 hour. Water was added and the mixture was extracted and washed with brine. Dried with MgSO₄, filtered and solvent evaporated. To the residue was added 30 mL of 0.5M NH₃ in dioxane and stirred 16 hours. The precipitate was filtered and the solvent evaporated. The residue was purified by MPLC (33% EtOAc in hexane) to afford the desired title compound as a beige solid (125 mg, 11%): mp 108-110 °C; ¹H NMR (CDCl₃) δ 0.85-0.93 (m, 6H), 1.13-1.59 (m, 10H), 1.60-1.67 (m, 1H), 1.94-2.20 (m, 5H), 2.82 (s, 6H), 2.99 (d, *J* = 15.3 Hz, 1H), 3.15 (t, *J* = 15.3 Hz, 1H), 3.23 (t, *J* = 7.7 Hz, 2H), 4.03 (t, *J* = 5.8 Hz, 2H), 4.08-4.10 (m, 1H), 4.79 (s, 2H), 5.47 (s, 1H), 6.02 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 1H). HRMS. Calc'd for C₃₀H₄₇N₂O₆S₂: 595.2876. Found: 595.2874.

[1156] Example 1406



[1157] (4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-azoniabicyclo[2.2.2]octane, methanesulfonate (salt)

[1158] Step 1: Preparation of dimesylate intermediate

[1159] To a cooled (-20 °C) solution of 5.0 g (65.7 mmol) of 1,3-propanediol in 50 mL of triethylamine and 200 mL of methylene chloride was added 15.8 g

(137.9 mmol) of methanesulfonyl chloride. The mixture was stirred for 30 minutes, then warmed to ambient temperature and partitioned between ethyl acetate and 1N HCl. The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo to give 13.5 g (89%) of dimesylate intermediate as a clear yellowish oil: ^1H NMR (CDCl_3) δ 2.12 (quintet, $J = 4.5$ Hz, 4H), 3.58 (s, 6H), 4.38 (t, $J = 5.4$ Hz)

[1160] Step 2: Preparation of propyl mesylate intermediate

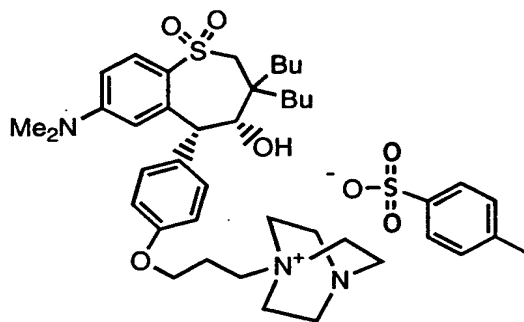
[1161] To a solution of 2.4 g (5.2 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenz-othiepine-1,1-dioxide (obtained from Example 1402, Step 10) and 6.0 g (26.1 mmol) of dimesylate intermediate (obtained from Step 1) in 50 mL of acetone was added 3.6 g (26.1 mmol) of K_2CO_3 . The reaction was heated to reflux overnight then cooled to ambient temperature and concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 36% ethyl acetate/hexanes afforded 2.8 g (90%) of the propyl mesylate intermediate as a white foam: ^1H NMR (CDCl_3) δ 0.86-0.95 (m, 6H), 1.06-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.14-2.32 (m, 3H), 2.84 (s, 6H), 3.02 (s, 3H), 3.08 (AB_q , $J_{\text{AB}} = 15.0$ Hz, $J = 46.9$ Hz, 4.09-4.18 (m, 3H), 4.48 (t, $J = 6.0$ Hz, 2H), 5.49 (s, 1H), 6.11 (s, 1H), 6.65 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 8.6$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.94 (d, $J = 8.9$ Hz, 1H).

[1162] Step 3: Preparation of quaternary salt

[1163] To a solution of 1.2 g (2.0 mmol) of propyl mesylate intermediate (obtained from Step 2) in 20 ml of acetonitrile was added 0.3g (2.9 mmol) of 1,4-diazabicyclo[2.2.2]octane (DABCO). The reaction mixture was stirred at 60°C for three hours, then cooled to ambient temperature and concentrated in vacuo. Purification by trituration with methylene chloride/ethyl ether gave 1.3 g (91%) of the desired title compound as a white solid: mp. (dec) $230-235^\circ\text{C}$; ^1H NMR (CDCl_3) δ 0.86-0.95 (m, 6H), 1.04-1.52 (m, 10H), 1.57-1.70 (m,

1H), 2.12-2.25 (m, 3H), 2.28-2.39 (m, 2H), 2.83 (s, 6H), 3.04 (s, 3H), 3.09 (AB_q, $J_{AB} = 15.6$ Hz, $J = 42.2$ Hz, 2H) 3.22-3.32 (m, 6H), 3.56-3.66 (m, 6H), 3.73-3.83 (m, 2H), 4.06-4.17 (m, 3H), 5.47 (s, 1H), 5.97 (s, 1H), 6.51 (d, $J = 8.6$ Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 2H), 7.41 (d, $J = 8.7$ Hz, 2H), 7.89 (d, $J = 8.9$ Hz, 1H). MS (ES+) m/e 612.4. HRMS (ES+) Calc'd for C₃₅H₅₄N₃O₄S⁺: 612.3835. Found: 612.3840.

[1164] Example 1407



[1165] (4R-cis)-1-[3-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]propyl]-4-aza-1-azoniabicyclo[2.2.2]octane,4-methylbenzenesulfonate (salt)

[1166] **Step 1: Preparation of propyl tosylate intermediate**

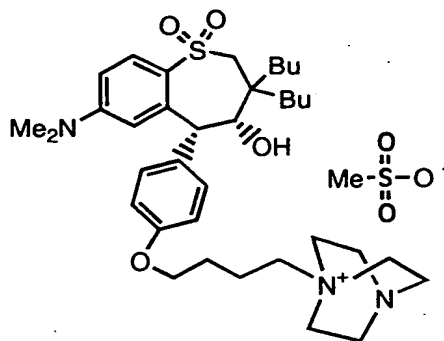
[1167] A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25°C under N₂ was treated with powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 eq.) and 1,3-propanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and the resulting mixture was stirred at 65°C for 21 hours. The cream-colored slurry was cooled to 25°C and was filtered through a sintered glass funnel. The filtrate was concentrated and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2 x 150 mL) and saturated aqueous NaCl (2 x 150 mL), and was dried (MgSO₄) and concentrated in vacuo to provide a pale orange oil. Purification by flash chromatography (4.4 x 35 cm silica, 20-30% EtOAc/hexane) afforded the propyl tosylate intermediate (6.0 g, 80%) as a white foam: ¹H NMR (CDCl₃) δ

0.91 (m, 6H), 1.11-1.47 (br m, 10H), 1.63 (m, 1H), 2.14 (m, 2H), 2.21 (m, 1H), 2.41 (s, 3H), 2.81 (s, 6H), 3.06 (ABq, $J = 15.1$ Hz, $J = 49.0$ Hz, 2H), 4.01 (t, $J = 5.3$ Hz, 2H), 4.10 (m, 1H), 4.26 (t, $J = 5.9$ Hz, 2H), 5.29 (s, 1H), 5.48 (s, 1H), 5.98 (s, 1H), 6.51 (dd, $J = 8.9$, 1.8 Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.88 (d, $J = 8.9$ Hz, 1H).

[1168] Step 2: Preparation of quaternary salt

[1169] A solution of the propyl tosylate intermediate (1.05 g, 1.56 mmol, obtained from Step 1) in acetonitrile (15 mL) at 25°C under N₂ was treated with diazabicyclo[2.2.2]octane (DABCO, 0.26 g, 2.34 mmol, 1.5 eq.) and stirred at 50°C for 6 hours, then at 25°C for 14 hours. The pale amber solution was cooled to 25°C and concentrated in vacuo to provide an amber oil. The residue was dissolved in a minimal amount of CH₂Cl₂ (5 mL) and diluted with Et₂O (100 mL) while vigorously stirring for 4 hours, during which time a white solid precipitated. The white solid was collected (Et₂O wash) to give the desired title compound (1.11 g, 90%) as a white amorphous solid: mp 136.5-142°C (decomposed); ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.12-1.43 (br m, 9H), 1.61 (m, 1H), 1.65 (m, 1H), 2.18 (m, 1H), 2.22 (m, 2H), 2.27 (s, 3H), 2.78 (s, 6H), 3.07 (ABq, $J = 15.1$ Hz, $J = 39.5$ Hz, 2H), 3.49 (br s, 6H), 3.68 (m, 1H), 3.74 (br s, 6H), 3.96 (br s, 2H), 4.09 (d, $J = 7.3$ Hz, 1H), 5.46 (s, 1H), 5.96 (d, $J = 2.4$ Hz, 1H), 6.49 (dd, $J = 8.9$, 2.4 Hz, 1H), 6.83 (d, $J = 8.5$ Hz, 2H), 7.11 (d, $J = 8.1$ Hz, 2H), 7.40 (d, $J = 8.3$ Hz, 2H), 7.74 (d, $J = 8.1$ Hz, 2H), 7.87 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for C₃₅H₅₄N₃O₄S: 612.3835. Found: 612.3832.

[1170] Example 1408



[1171] (4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-azoniabicyclo[2.2.2]octanemethanesulfonate (salt)

[1172] **Step 1: Preparation of butyl mesylate intermediate**

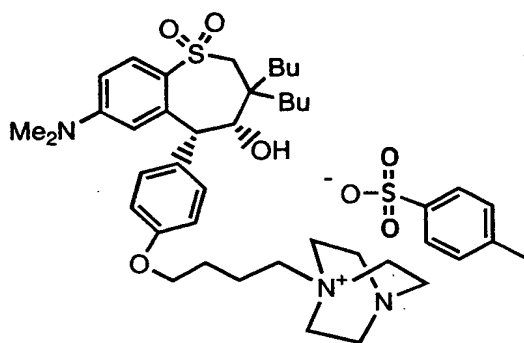
[1173] A mixture of 1.00 g (2.18 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Example 1402, Step 10), 2.68 g (10.88 mmol) of busulfan, and 1.50 g (10.88 mmol) of potassium carbonate in 20 mL of acetone was stirred at reflux overnight. The mixture was concentrated in vacuo and the crude was dissolved in 30 mL of ethyl acetate. The insoluble solid was filtered off and the filtrate was concentrated in vacuo. The resulting white foam was chromatographed through silica gel column, and eluted with 30% ethyl acetate/hexane to give 1.02 g (77%) of butyl mesylate intermediate as a white solid: ¹H NMR (CDCl₃) δ 0.90 (m, 6H), 1.20-1.67 (m, 12H), 1.98 (m, 4H), 2.22 (m, 1H), 2.83 (s, 6H), 3.04 (s, 3H), 3.08 (ABq, 2H), 4.05 (t, *J* = 5.55 Hz, 2H), 4.11 (d, *J* = 6.90 Hz, 1H), 4.35 (t, *J* = 6.0 Hz, 2H), 5.49 (s, 1H), 6.00 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 9.0 Hz, 2.7 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 1H).

[1174] **Step 2: Preparation of ester intermediate**

[1175] A solution of 520 mg (0.85 mmol) of butyl mesylate intermediate (obtained from Step 1) and 191 mg (1.71 mmol) of DABCO in 10 mL of acetonitrile was stirred at 80°C for 4 hours. The reaction mixture was concentrated in

vacuo to yield a white foam. The foam was crushed and washed with ether. The solid was filtered off and dried in vacuo to give 540 mg (88%) of the desired title compound which was recrystallized from methylene chloride and acetone as a white solid: mp 248-251 °C; ¹H NMR (CDCl₃) δ 0.91 (m, 6H), 1.14-1.47 (m, 14H), 1.63 (m, 1H), 1.96 (m, 4H), 2.21 (m, 1H), 2.77 (s, 3H), 2.82 (s, 3H), 3.07 (ABq, 2H), 3.26 (t, *J* = 7.1 Hz, 6H), 3.60 (m, 8H), 4.08 (m, 3H), 5.47 (s, 1H), 5.99 (d, *J* = 2.4 Hz, 1H), 6.51 (dd, *J* = 8.9 Hz, 2.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 1H).

[1176] Example 1409



[1177] (4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-4-aza-1-azoniabicyclo[2.2.2]octane-4-methylbenzenesulfonate (salt)

[1178] **Step 1: Preparation of propyl tosylate intermediate**

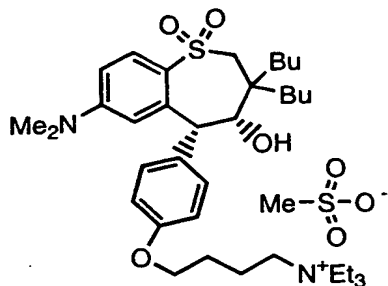
[1179] A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25°C under N₂ was treated with powdered K₂CO₃ (3.8 g, 27.2 mmol, 2.5 eq.) and 1,4-butanediol di-*p*-tosylate (13.0 g, 32.6 mmol, 3.0 eq.), and the resulting solution was stirred at 65°C for 21 hours. The cream-colored slurry was cooled to 25°C and filtered through a sintered glass funnel. The filtrate was concentrated and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with saturated aqueous NaHCO₃ (2 x 150 mL) and saturated aqueous NaCl (2 x 150 mL). The extract was dried (MgSO₄) and concentrated

in vacuo to provide a pale orange oil. Purification by flash chromatography (4.4 x 35 cm silica, 20-30% EtOAc/hexane) afforded the propyl tosylate intermediate (6.0 g, 80%) as a white foam: ^1H NMR (CDCl_3) δ 0.89 (m, 6H), 1.10-1.44 (br m, 10H), 1.61 (m, 1H), 1.84 (m, 4H), 2.19 (m, 1H), 2.43 (s, 3H), 2.80 (s, 6H), 3.03 (ABq, $J = 15.1$ Hz, $J = 46.3$ Hz, 2H), 3.93 (m, 2H), 4.06-4.13 (m, 4H), 5.44 (s, 1H), 5.96 (s, 1H), 6.46 (dd, $J = 8.9$, 1.4 Hz, 1H), 6.85 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.78 (d, $J = 8.9$ Hz, 2H), 7.83 (m, 1H).

[1180] Step 2: Preparation of quaternary salt

[1181] A solution of propyl tosylate intermediate (5.8 g, 8.5 mmol, obtained from Step 1) in acetonitrile (100 mL) at 25°C under N_2 was treated with diazabicyclo[2.2.2]octane (DABCO, 1.1 g, 10.1 mmol, 1.2 eq.) and stirred at 45°C for 6 hours. The pale yellow solution was cooled to 25°C and concentrated in vacuo to provide an off-white solid. The residue was dissolved in a minimal amount of CH_2Cl_2 (5 mL) and diluted with Et_2O (100 mL) while vigorously stirring for 3 hours, during which time a white solid precipitated. The white solid was collected and recrystallized from EtOAc/hexane to give the desired title compound (5.7 g, 85%) as colorless needles: mp 223-231°C (decomposed); ^1H NMR (CDCl_3) δ 0.86 (m, 6H), 1.09-1.43 (br m, 12H), 1.61-1.90 (br m, 5H), 2.13 (m, 1H), 2.25 (s, 3H), 2.75 (s, 6H), 3.03 (ABq, $J = 15.1$ Hz, $J = 30.0$ Hz, 2H), 3.05 (br s, 6H), 3.37 (br s, 6H), 3.89 (m, 2H), 4.07 (d, $J = 7.5$ Hz, 1H), 5.39 (s, 2H), 5.97 (d, $J = 1.6$ Hz, 1H), 6.44 (dd, $J = 8.9$, 2.0 Hz, 1H), 6.87 (d, $J = 8.3$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.80 (d, $J = 8.9$ Hz, 1H); HRMS. Calc'd for $\text{C}_{36}\text{H}_{56}\text{N}_3\text{O}_4\text{S}$: 626.3992. Found: 626.3994. Anal. Calc'd for $\text{C}_{43}\text{H}_{63}\text{N}_3\text{O}_7\text{S}_2$: C, 64.71; H, 7.96; N, 5.27. Found: C, 64.36; H, 8.10; N, 5.32.

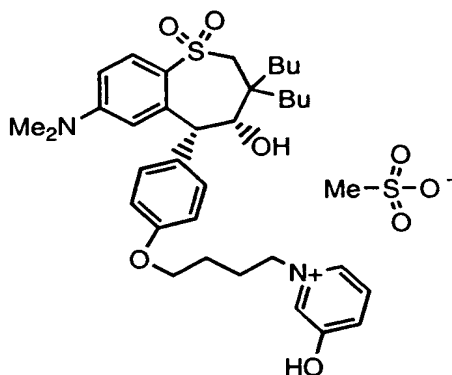
[1182] Example 1410



[1183] (4R-cis)-4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]-N,N,N-triethyl-1-butanaminium

[1184] A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 15 mL of triethylamine in 10 mL of acetonitrile was heated at 50°C for 2 days. The solvent was evaporated and the residue was triturated with ether and ethyl acetate to afford 500 mg (43%) of product as a semi-solid. ¹H NMR (CDCl₃) δ 0.8 (m, 6 H), 1-1.6 (m, 24 H), 2.1 (m, 1 H), 2.6 (s, 3 H), 2.7 (s, 6 H), 2.9 (d, J = 15 Hz, 1 H), 3.0 (d, J = 15 Hz, 1 H), 3.3 (m, 8 H), 4.0 (m, 4 H), 5.3 (s, 1 H), 5.9 (s, 1 H), 6.4 (m, 1 H), 6.8 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS *m/e* 615.

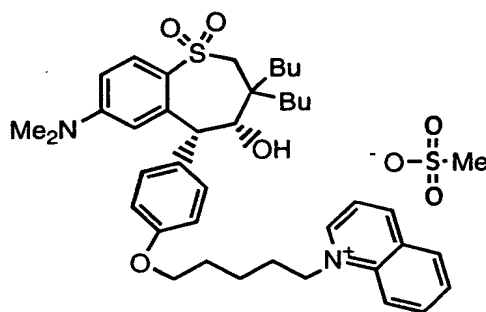
[1185] Example 1411



[1186] (4R-cis)-1-[4-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]butyl]-3-hydroxypyridinium, methanesulfonate (salt)

[1187] A solution of 1 g (1.64 mmol) of the butyl mesylate intermediate (obtained from Example 1408, Step 1) and 234 mg (2.46 mmol) of 3-hydroxy pyridine in 1 mL of dimethylformamide was heated at 70°C for 20 hours. The solvent was evaporated and the residue was triturated with ether and ethyl acetate to afford 990 mg (86%) of product as a semi-solid: ^1H NMR (CDCl_3) δ 0.9 (m, 6 H), 1-1.5 (m, 10 H), 1.7 (m, 1 H), 1.9 (m, 2 H), 2-2.4 (m, 3 H), 2.9 (s, 6 H), 3.1 (d, $J = 15$ Hz, 1 H), 3.2 (d, $J = 15$ Hz, 1 H), 4.1 (m, 3 H), 4.7 (m, 2 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, $J = 9$ Hz, 2 H), 7.4 (d, $J = 9$ Hz, 2 H), 7.7 (m, 1 H), 8.0 (m, 2 H), 8.2 (m, 1 H), 9.1 (s, 1 H). MS m/e 609.

[1188] Example 1412



[1189] (4R-cis)-1-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]quinolinium, methanesulfonate (salt)

[1190] **Step 1: Preparation of pentyl mesylate intermediate**

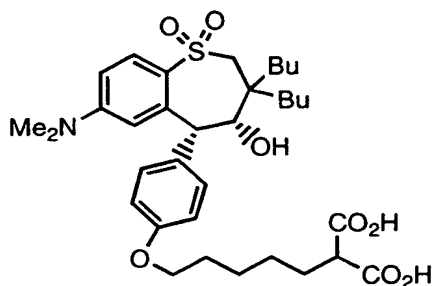
[1191] To a stirred solution of 231 mg (5.79 mmol, 60% disp.) of NaH in 22 mL of DMF was added 2.05g (4.45 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-hydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the mixture was added 18.02 g (55.63 mmol) of 1,5-diiodopentane and the solution was stirred overnight at ambient temperature. DMF was removed by high vacuum and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO_4 , and the concentrated residue was purified by column chromatography to give the pentyl mesylate intermediate: ^1H NMR (CDCl_3) δ

0.90(q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6h), 3.0 (q, 2H), 3.22 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.1 (d, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

[1192] Step 2: Preparation of quaternary salt

[1193] To 1.0g (1.53 mmol) of the pentyl mesylate intermediate (obtained from Step 1) was added 3.94 g (30.5 mmol) of quinoline and 30 mL of acetonitrile. The solution was heated at 45°C under N₂ for 10 days. The concentrated residue was purified by reverse phase C18 column chromatography. The obtained material was exchanged to its mesylate anion by ion exchange chromatography to give the desired title compound as a solid: mp 136 °C; ¹H NMR (CDCl₃) δ 0.95(q, 6H), 1.05-2.25 (m, 18H), 2.8 (s, 9H), 3.0 (q, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.28 (t, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.45 (d, 1H), 6.82 (d, 2H), 7.4 (d, 2H), 7.82 (d, 1H), 7.9 (t, 1H), 8.2 (t, 2H), 8.3 (q, 2H), 8.98 (d, 1H), 10.2 (d, 1H). HRMS. Calc'd for C₄₀H₅₃N₂O₄S: 657.3726. Found: 657.3736. Anal. Calc'd for C₄₀H₅₃N₂O₄S·CH₃O₃S: C, 65.40; H, 7.50; N, 3.72; S, 8.52. Found: C, 62.9; H, 7.42; N, 3.56; S, 8.41.

[1194] Example 1413



[1195] (4S-cis)-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]propanedioic acid

[1196] Step 1: Preparation of pentyl bromide intermediate

[1197] To a stirred solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was added 6.0 g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-hydrobenzothiepine-1,1-dioxide (obtained from

Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and the mixture was stirred overnight at ambient temperature. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO_4 , and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: ^1H NMR (CDCl_3) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

[1198] Step 2: Preparation of dibenzyl ester intermediate

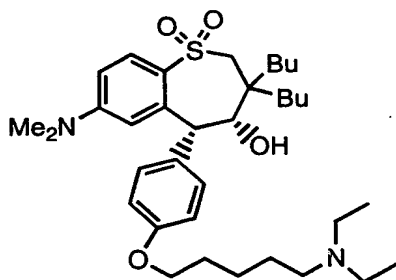
[1199] To the mixture of 59 mg (1.476 mmol, 60% disp) of NaH in 27 mL of THF and 9 mL of DMF at 0°C was added 0.84 g (2.952 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min. To the solution was added 0.5987 g (0.984 mmol) of the pentyl bromide intermediate, and the mixture was stirred at 80°C overnight. Solvent was removed in vacuo, and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO_4 , and the concentrated residue was purified by column chromatography to give the dibenzyl ester intermediate: ^1H NMR (CDCl_3) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 1H), 3.9 (t, 2H), 4.1 (d, 1H), 5.18 (s, 4H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.2-7.4 (m, 12H), 7.85 (d, 1H).

[1200] Step 3: Preparation of diacid

[1201] A suspension of 0.539 g (0.664 mmol) of the dibenzyl ester intermediate (obtained from Step 2) and 25 mg of 10% Pd/C in 30 mL of ethanol was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 118°C ; ^1H NMR (CDCl_3) δ 0.9 (d, 6H), 1.05-2.2 (m, 20H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 1H), 3.95 (s, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.85 (d, 1H).

HRMS. Calc'd for $C_{34}H_{49}NO_8S$: 632.3257. Found: 632.3264. Anal. Calc'd for $C_{34}H_{49}NO_8S$: C, 64.63; H, 7.82; N, 2.22; S, 5.08. Found: C, 63.82; H, 7.89; N, 2.14; S, 4.93.

[1202] Example 1414



[1203] (4R-cis)-3,3-Dibutyl-5-[4-[[5-(diethylamino)pentyl]oxy]phenyl]-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-dioxide

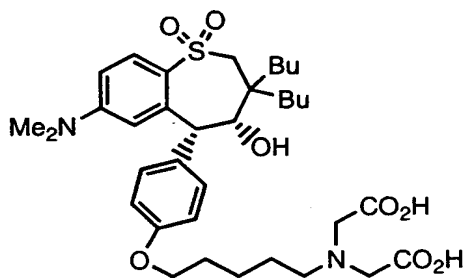
[1204] **Step 1: Preparation of pentyl iodide intermediate**

[1205] To a solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (3 g, 6.53 mmol, obtained from Example 1402, Step 10) in 100 mL of dimethylformamide was added 198 mg (7.83 mmol) of 95% sodium hydride. The mixture was stirred 15 minutes at room temperature and diiodopentane was added. After one hour at room temperature the mixture was diluted in ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel, eluting with hexane/ethyl acetate (1/5) to afford 2.92g (4.46 mmol) of the pentyl iodide intermediate: 1H NMR ($CDCl_3$) δ 0.9 (m, 6 H), 1-1.5 (m, 11 H), 1.6 (m, 3 H), 1.8 (m, 4 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (d, J = 15 Hz, 1 H), 3.2 (d, J = 15 Hz, 1 H), 3.3 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.5 (s, 1 H), 6.1 (s, 1 H), 6.6 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.9 (d, J = 7 Hz, 1 H).

[1206] Step 2: Preparation of amine

[1207] A solution of 550 mg (0.76 mmol) of the pentyl iodide intermediate (obtained from Step 1) and 279 mg (3.81 mmol) of diethylamine in 3 mL of acetonitrile was stirred at 100°C overnight. The mixture was concentrated in vacuo to yield a yellowish brown foam. The foam was dissolved in 10 mL of ethyl acetate and washed with 50 mL of saturated sodium carbonate solution twice. The ethyl acetate layer was dried over magnesium sulfate and concentrated to yield 390 mg (85%) of the desired title compound as a yellow foamy solid: ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.20-1.47 (m, 12H), 1.53-1.67 (m, 4H), 1.76-1.90 (m, 8H), 2.21 (m, 1H), 2.74-2.92 (m, 12H), 3.07 (ABq, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 4.10 (d, *J* = 7.8 Hz, 1H), 5.48 (s, 1H), 6.00 (d, *J* = 2.4 Hz, 1H), 6.51 (dd, *J* = 9.2 Hz, 2.6 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 1H).

[1208] Example 1415



[1209] (4R-cis)-N-(Carboxymethyl)-N-[5-[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine

[1210] Step 1: Preparation of diester intermediate

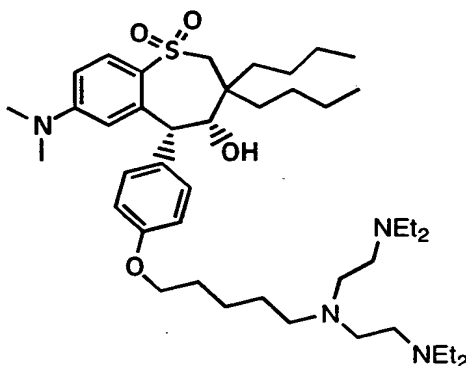
[1211] A mixture of 8.6 g (14.1 mmol) of pentyl bromide intermediate (obtained from Example 1413, Step 1), 65 g (0.35 mol) of diethylaminodiacetate and 7.5 g (71 mmol) of anhydrous Na₂CO₃ was stirred at 160°C for 3 hours. The reaction mixture was diluted with water and extracted with methylene chloride. The volatiles was removed in vacuo to give 9.6g (95%) of the

diester intermediate. ^1H NMR spectrum was consistent with the structure; MS (M+H) m/e 717.

[1212] Step 2: Preparation of diacid

[1213] The mixture of the diester intermediate (obtained from Step 1) and 2.7g (64.3 mmol) of LiOH in THF (75 mL) and water (50 mL) was stirred at 40°C for 18 hours. The reaction mixture was acidified with 1% HCl and extracted with dichloromethane. The residue was triturated with hexane, filtered to give 8.9g (93%) of the desired title compound as a solid: mp 148-162 °C; ¹H NMR (CD₃OD) δ 0.92 (t, 6H), 1.1-1.9 (m, 31H), 2.15 (t, 1H), 2.8(s, 6H), 3.15 (ABq, 2H), 3.75(m, 1H), 4.1 (m, 6H), 5.3(s, 1H), 6.1 (s, 1H), 6.6 (d, 1H), 7.0(d, 2H), 7.4 (d, 2H), 7.8 (d, 1H); MS (M+H) *m/e* 661. Anal. Calc'd for [C₃₅H₅₂N₂O₈S + 1.5H₂O]: C,61.11; H,8.06; N,4.07; S,4.66. Found: C,61.00; H,7.72; N,3.89; S,4.47.

[1214] Example 1416

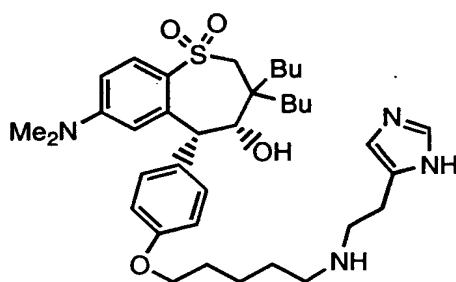


[1215] (4R-cis)-5-[4-[[5-[bis[2-(Diethylamino)ethyl]amino]pentyl]oxy]phenyl]-3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-1-benzothiepin-4-ol 1,1-dioxide

[1216] A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) in N,N,N',N'-tetraethyl diethylenetriamine was heated to 80°C for 4 hours. The mixture was dissolved in ethyl acetate and saturated NaHCO₃. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by reverse phase

chromatography. The fractions containing the product were concentrated in vacuo, dissolved in ethyl acetate and washed with saturated NaHCO₃. The residue was dried and concentrated in vacuo to afford 840 mg (74%) of the desired title compound as a thick oil. ¹H NMR (CDCl₃) δ 0.8 (m, 6 H), 1-1.6 (m, 28 H), 1.8 (m, 2 H), 2.1 (m, 1 H), 2.5 (m, 18 H), 2.7 (s, 6 H), 2.9 (d, J = 15 Hz, 1 H), 3.1 (d, J = 15 Hz, 1 H), 3.9 (m, 2 H), 4.0 (m, 1 H), 4.1 (s, 1 H), 5.4 (s, 1 H), 6.0 (s, 1 H), 6.4 (m, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (d, J = 9 Hz, 2 H), 7.8 (d, J = 7 Hz, 1 H). MS (M+H) *m/e* 743.

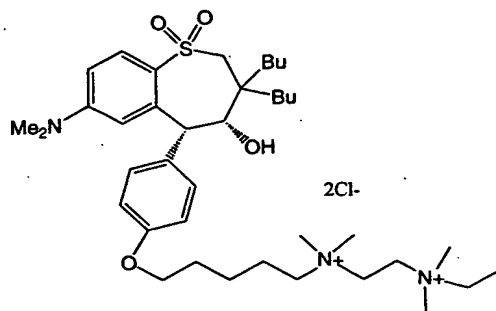
[1217] Example 1417



[1218] (4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-[[2-(1H-imidazol-4-yl)ethyl]amino]pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

[1219] A solution of 1 g of pentyl iodide intermediate (1.53 mmol, obtained from Example 1414, Step 1) and 3.4 g (30.6 mmol) of histamine was heated to 50°C for 17 hours. The mixture was dissolved in ethyl acetate and saturated NaHCO₃. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was triturated with ether to afford 588 mg (60%) of the desired title compound as a semi-solid: ¹H NMR (CDCl₃) δ 0.9 (m, 6 H), 1-1.7 (m, 14 H), 1.9 (m, 3 H), 2.0 (m, 2 H), 2.2 (m, 1 H), 2.8 (s, 6 H), 3.0 (m, 3 H), 3.2 (m, 2 H), 4.0 (m, 2 H), 4.1 (m, 3 H), 5.5 (s, 1 H), 6.0 (s, 1 H), 6.5 (m, 1 H), 6.8 (s, 1 H), 6.9 (d, J = 9 Hz, 2 H), 7.4 (m, 3 H), 7.9 (d, J = 8 Hz, 1 H). MS (M+H) *m/e* 639.

[1220] Example 1418



[1221] (4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]-N'-ethyl-N,N,N',N'-tetramethyl-1,2-ethanediaminium dichloride

[1222] Step 1: Preparation of pentyl bromide intermediate

[1223] A mixture of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1.680g, 3.66 mmol, obtained from Example 1402, Step 10) and sodium hydride (0.250g, 6.25 mmol) in 30 mL of DMF was stirred in a dry 100 mL round-bottom flask under N₂. To this solution was added 1,5-dibromopentane (6.0 mL/44.0 mmol), and the resulting mixture was stirred for 18 hours. The reaction was diluted with brine (100 mL) and H₂O (20 mL), and the mixture was extracted with EtOAc (3x50 mL). Organic layers were combined, dried (MgSO₄), filtered and concentrated in vacuo. Purification by filtration through silica gel eluting with 20% EtOAc/hexane and evaporation in vacuo gave pentyl bromide intermediate as a white foamy solid (1.783g, 80%): ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.56 (m, 10H), 1.58-1.70 (m, 3H), 1.78-2.03 (m, 4H), 2.15-2.24 (m, 1H), 2.77 (s, 1H), 2.80 (s, 6H), 3.05 (ABq, 2H), 3.42 (t, 2H), 3.98 (t, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 5.99 (d, 1H), 6.50 (dd, 1H), 6.91 (d, 2H), 7.40 (d, 2H), 7.88 (d, 1H).

[1224] Step 2: Preparation of mono-quaternary salt

[1225] The mixture of pentyl bromide intermediate (0.853g, 1.40 mmol, obtained from Step 1), N,N,N',N'-tetramethylethylenediamine (1.0 mL/6.62 mmol) in 30 mL of acetonitrile was stirred at 40°C for 12 hours, and the reaction mixture was concentrated in vacuo to give an off-white foamy solid (1.052g).

The crude product was dissolved in acetonitrile (1.5 mL) and triturated with ethyl ether. The solvent was decanted to yield a sticky solid. This trituration method was repeated twice, and the resulting sticky solid was concentrated in vacuo to give the mono-quaternary salt as an off-white foamy solid (0.951g, 94%): ^1H NMR (CDCl_3) δ 0.81 (t, 6H), 0.96-1.64 (m, 13H), 1.62-1.85 (m, 4H), 2.03-2.18 (m, 1H), 2.20 (s, 6H), 2.67 (t, 2H), 2.74 (s, 6H), 2.98 (ABq, 2H), 3.30-3.42 (m, 1H), 3.38 (s, 6H), 3.60-3.75 (m, 4H), 3.90 (t, 2H), 4.01 (s, 1H), 5.37 (s, 1H), 5.92 (s, 1H), 6.41 (dd, 1H), 6.81 (d, 2H), 7.32 (d, 2H), 7.77 (d, 1H).

[1226] Step 3: Preparation of di-quaternary salt

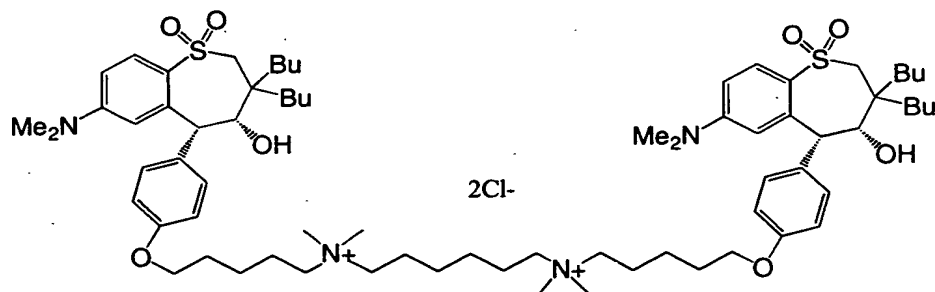
[1227] The mono-quaternary salt (0.933g, 1.29 mmol, obtained from Step 2), iodoethane (0.300 mL/3.75 mmol), and acetonitrile (30.0 mL) were combined in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N_2 , sealed, equipped with magnetic stirrer, and heated to $50\text{ }^\circ\text{C}$. After 24 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give a yellow foamy solid (1.166g). The solid was dissolved in methylene chloride/acetonitrile and precipitated with ethyl ether. After cooling to $0\text{ }^\circ\text{C}$ overnight, the resulting solid was filtered, washed with ethyl ether and concentrated in vacuo to yield the di-quaternary salt as an off-white solid (1.046g, 92%): ^1H NMR (CD_3OD) δ 0.59 (t, 6H), 0.70-1.10 (m, 9H), 1.16 (t, 3H), 1.22-1.80 (m, 9H), 2.42 (s, 6H), 2.78 (d, 2H), 2.98 (s, 6H), 3.02 (s, 6H), 3.22-3.37 (m, 4H), 3.63-3.78 (m, 4H), 3.80 (s, 4H), 4.93 (s, 1H), 5.71 (s, 1H), 6.22 (dd, 1H), 6.61 (d, 2H), 7.02 (d, 2H), 7.40 (d, 1H).

[1228] Step 4: Preparation of quaternary di-chloride salt

[1229] The iodobromosalt (obtained from Step 3) was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H_2O /acetonitrile to give the desired title compound as a white foamy solid (0.746g, 84%): mp $193.0\text{--}197.0\text{ }^\circ\text{C}$; ^1H NMR (CD_3OD) δ 0.59 (t, $J = 6.0\text{ Hz}$, 6H), 0.70-1.12 (m, 9H), 1.16 (t, $J = 6.6\text{ Hz}$, 3H), 1.24-1.90 (m, 9H), 2.50 (s, 6H), 2.78 (s, 2H), 3.08 (s, 6H), 3.11 (s, 6H), 3.24-3.50 (m, 4H), 3.68 (s, 2H),

3.81 (s, 2H), 4.16 (s, 4H), 5.02 (s, 1H), 5.72 (s, 1H), 6.19 (d, $J = 8.4$ Hz, 1H), 6.61 (d, $J = 8.1$ Hz, 2H), 7.10 (d, $J = 7.8$ Hz, 2H), 7.46 (d, $J = 8.7$ Hz, 1H).
HRMS. Calc'd for $C_{39}H_{67}N_3O_4SCl$: 708.4541. Found: 708.4598.

[1230] Example 1419

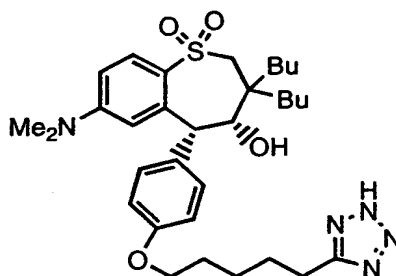


[1231] **[4R-[4a,5a(4R*,5R*)]]-N,N'-bis[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]-N,N,N',N'-tetramethyl-1,6-hexanediaminium dichloride**

[1232] The pentyl bromide intermediate (1.002g, 1.64 mmol, obtained from Example 1418, Step 1) and N,N,N',N'-tetramethyl-1,6-hexanediamine (0.100g, 0.580 mmol) in 5 mL of acetonitrile were placed in a 4 oz. Fischer Porter bottle. The reaction vessel was purged with N_2 , sealed, equipped with magnetic stirrer and heated to 50 °C. After 15 hours, the reaction mixture was cooled to ambient temperature and concentrated in vacuo to give an off-white foamy solid (1.141g). The solid was dissolved in acetonitrile and precipitated with ethyl ether. After cooling to 0 °C, the solvent was decanted to yield a sticky off-white solid. This trituration method was repeated, and the resulting sticky solid was concentrated in vacuo to give the desired dibromide salt as an off-white foamy solid (0.843g, quantitative): 1H NMR ($CDCl_3$) δ 0.85 (m, 12H), 1.01-1.70 (m, 30H), 1.76-2.08 (m, 12H), 2.18 (t, $J = 12.3$ Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.35 (s, 12H), 3.52 (br s, 6H), 3.72 (br s, 4H), 3.97 (br s, 4H), 4.08 (br s, 2H), 5.42 (s, 2H), 6.00 (s, 2H), 6.51 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 7.8$ Hz, 4H), 7.38 (d, $J = 7.8$ Hz, 4H), 7.83 (d, $J = 8.7$ Hz, 2H). The dibromide salt was converted to its corresponding dichloride salt using Biorad AG 2X8 resin and eluting with 70% H_2O/CH_3CN to give the desired

title compound as a white foamy solid (0.676g, 86%): mp 178.0-182.0 °C; ¹H NMR (CDCl₃) δ 0.80-0.90 (m, 12H), 1.01-1.70 (m, 30H), 1.75-2.06 (m, 12H), 2.16 (t, *J* = 12.9 Hz, 2H), 2.79 (s, 12H), 3.03 (ABq, 4H), 3.33 (s, 12H), 3.49 (br s, 6H), 3.70 (br s, 4H), 3.96 (t, *J* = 5.4 Hz, 4H), 4.08 (s, 2H), 5.42 (s, 2H), 5.986 (s, 1H), 5.993 (s, 1H), 6.49 (d, *J* = 9.0 Hz, 1H), 6.50 (d, *J* = 9.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 4H), 7.38 (d, *J* = 8.1 Hz, 4H), 7.84 (d, *J* = 8.7 Hz, 2 H). HRMS. Calc'd for C₃₆H₅₈N₂O₄S: 614.4118. Found: 614.4148.

[1233] Example 1420



[1234] (4R-cis)-3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-5-[4-[[5-(1H-tetrazol-5-yl)pentyl]oxy]phenyl]-1-benzothiepin-4-ol 1,1-dioxide

[1235] **Step 1: Preparation of pentyl bromide intermediate**

[1236] To a stirred suspension of 1.01 g (25.4 mmol, 60% oil dispersion) of sodium hydride in 150 mL of DMF was added 9.0g (19.5 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in portions. After 30 minutes the reaction was cooled in a water bath (15 °C) and 4.48 g (195 mmol) of 1,5-dibromopropane was added. The reaction was stirred at ambient temperature for 1.5 hours and quenched with 50 mL of saturated NH₄Cl. The reaction was diluted with ethyl acetate, washed with water, brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-Prep 500) using 25% ethyl acetate/hexanes afforded 10.17 g (85%) of the pentyl bromide intermediate as a colorless foam: mp 65-70 °C; ¹H NMR (CDCl₃) δ 0.84-0.98 (M, 6H), 1.04-1.52 (m, 10H), 1.58-1.65 (m, 3H), 1.82 (p, *J* = 6.8 Hz, 2H), 1.94 (p, *J* = 7.0 Hz, 2H), 2.12-2.26 (m, 1H), 2.82 (s, 6H), 3.06

(AB_q, $J_{AB} = 15.2, 45.3$ Hz, 2H), 3.44 (t, $J = 6.7$ Hz, 2H), 3.99 (t, $J = 6.3$ Hz, 2H), 4.10 (s, 1H), 5.47 (s, 1H), 6.15 (d, $J = 2.7$ Hz, 1H), 6.68 (dd, $J = 2.5, 8.4$ Hz, 1H), 6.91 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.93 (d, $J = 8.7$ Hz, 1H).

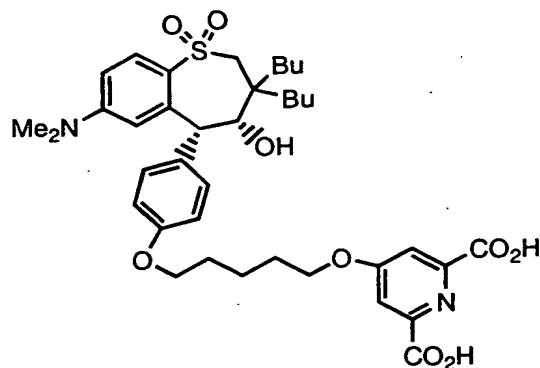
[1237] Step 2: Preparation of pentyl nitrile intermediate

[1238] To a stirred solution of 378 mg (0.621 mmol) of the pentyl bromide intermediate (obtained from Step 1) in 1 mL of DMSO was added 37 mg (0.745 mmol) of sodium cyanide. The reaction was stirred at ambient temperature for 16 hours. The reaction was concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated in vacuo to afford 278 mg (93% RPHPLC purity, ca. 75%) of the pentyl nitrile intermediate as a colorless foam: ¹H NMR (CDCl₃) δ 0.86-0.96 (m, 6H), 1.02-1.21 (m, 1H), 1.21-1.52 (m, 19H), 1.58-1.92 (m, 7H), 2.16-2.28 (m, 1H), 2.41 (t, $J = 6.9$ Hz, 2H), 2.83 (s, 6H), 3.08 (AB_q, 15.0, 47.5 Hz, 2H), 4.01 (t, $J = 6.2$ Hz, 2H), 4.1 (s, 1H), 5.49 (s, 1H), 6.07 (d, $J = 2.1$ Hz, 1H), 6.59 (dd, $J = 2.4, 8.7$ Hz, 1H), 6.92 (d, $J = 8.1$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.7$ Hz, 1H). MS (ES, M+H) m/e 555.

[1239] Step 3: Preparation of tetrazole

[1240] A solution of 275 mg (0.5 mmol) of the nitrile intermediate (obtained from Step 2) and 666 mg (3.23 mmol) of azidotrimethyltin in 5 mL of toluene was stirred with heating at 80°C for 60 hours. The reaction was concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 226 mg of the desired title compound (75%) as a colorless foam: mp 80-85 °C; ¹H NMR (CDCl₃) δ 0.83-0.95 (m, 6H), 1.30-1.52 (m, 10H), 1.52-1.73 (m, 3H), 1.79-1.99 (m, 4H), 2.14-2.26 (m, 1H), 2.91 (s, 6H), 3.02-3.22 (m, 4H), 3.92-4.06 (m, 2H), 4.16 (s, 1H), 5.47 (s, 1H), 6.28 (d, $J = 2.4$ Hz, 1H), 6.74 (dd, $J = 2.7, 8.8$ Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.98 (d, $J = 8.7$ Hz, 1H). HRMS Calc'd for C₃₂H₄₈N₅O₄S: 598.3427. Found: 598.3443.

[1241] Example 1421



[1242] (4R-cis)-4-[[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1H-benzothiepin-5-yl]phenoxy]pentyl]oxy]-2,6-pyridinedicarboxylic acid

[1243] **Step 1: Preparation of pentyl bromide intermediate**

[1244] To a solution of 0.63 g (15.72 mmol, 60% disp) of NaH in 85 mL of DMF was added 6.0 g (13.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 1 hour. To the solution was added 37.7 g (163.75 mmol) of 1,5-dibromopentane, and stirred overnight at ambient temperature. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pentyl bromide intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (t, 2H), 3.95 (t, 2H), 4.1 (s, 1H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

[1245] **Step 2: Esterification of chelidamic acid**

[1246] A solution of 10 g (54.6 mmol) of chelidamic acid, 23.0 g (120.12 mmol) of 1-(3-dimethyl amino propyl)-3 ethyl carbodiimide hydrochloride, 1.33 g (10.8 mmol) of 4-dimethyl amino pyridine, and 12.4 mL (120.12 mmol) of benzyl alcohol in 100 mL of DMF was stirred at ambient temperature overnight under

N₂. DMF was removed in vacuo and the residue was extracted with methylene chloride, washed with 5% NaHCO₃, 5% acetic acid, H₂O, and brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give dibenzyl chelidamic ester: ¹H NMR (CDCl₃) δ 5.4 (s, 4H), 7.4 (m, 12H).

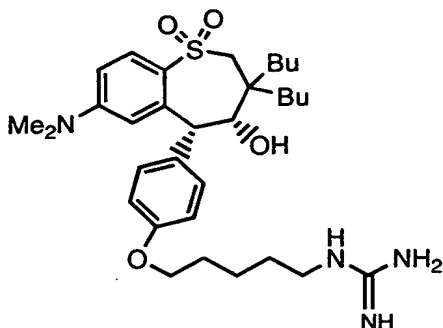
[1247] Step 3: Preparation of pyridinyl benzyl ester intermediate

[1248] A solution of 79 mg (1.972 mmol, 60% disp) of NaH and 0.716g (1.972 mmol) of dibenzyl chelidamic ester (obtained from Step 2) in 17.5 mL of DMF was stirred at ambient temperature for 1 hour. To the solution was added 1.0 g (1.643 mmol) of the pentyl bromide intermediate and the mixture was stirred under N₂ overnight at 40 °C. DMF was removed in vacuo, and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the pyridinyl dibenzyl ester intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6H), 1.05-2.0 (m, 19H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 4.0 (t, 2H), 4.1 (s, 1H), 5.4 (s, 4H), 5.42 (s, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3-7.5 (m, 12H), 7.78 (s, 2H), 7.9 (d, 1H).

[1249] Step 4: Preparation of pyridinyl diacid

[1250] A suspension of 0.8813 g (0.99 mmole) of dibenzyl ester (obtained from Step 3) and 40 mg of 10% Pd/C in 35 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 143 °C; ¹H NMR (THF-d₈) 0.95 (q, 6H), 1.05-1.65 (m, 15H), 1.9 (m, 4H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 4.1 (s, 3H), 4.3 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.78 (d, 1H), 7.82 (s, 2H). HRMS. Calc'd for C₃₈H₅₀N₂O₉S: 711.3315. Found: 711.3322. Anal. Calc'd for C₃₈H₅₀N₂O₉S: C, 64.20; H, 7.09; N, 3.94; S, 4.51. Found: C, 62.34; H, 6.97; N, 4.01; S, 4.48.

[1251] Example 1422



[1252] (4R-cis)-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]guanidine

[1253] **Step 1: Preparation of pentyl azide intermediate**

[1254] To a stirred solution of 200 mg (0.328 mmol) of the pentyl bromide intermediate (obtained from Example 1420, Step 1) in 0.75 mL of DMSO was added 32 mg (0.493 mmol) of sodium azide and a catalytic amount of sodium iodide. The reaction was stirred at ambient temperature for 64 hours. The reaction was concentrated under a nitrogen stream and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated in vacuo to afford 155 mg (92% RPHPLC purity, about 76% yield) of the pentyl azide intermediate as a colorless foam. Sample was used without further purification: mp 45-50 °C; ^1H NMR (CDCl_3) δ 0.83-0.93 (m, 6H), 1.03-1.48 (m, 10H), 1.54-1.74 (m, 5H), 1.78-1.86 (m, 1H), 2.14-2.26 (m, 1H), 2.81 (s, 6H), 3.06 (AB_q , $J_{\text{AB}} = 15.0, 48.0$ Hz, 2H), 3.31 (t, $J = 6.3$ Hz, 2H), 3.98 (t, $J = 6.3$ Hz, 2H), 4.09 (s, 1H), 5.47 (s, 1H), 6.10 (d, $J = 1.8$ Hz, 1H), 6.63 (dd, $J = 2.7, 9.0$ Hz, 1H), 6.91 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 1H). MS (FAB, $\text{M}+\text{H}$) m/e 571.

[1255] **Step 2: Preparation of pentyl amine intermediate**

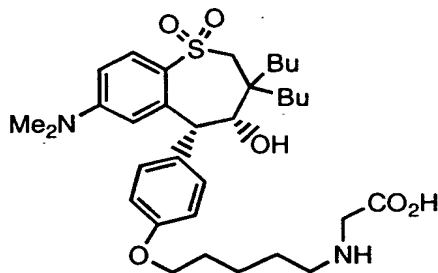
[1256] To a solution of 0.67 g (1.17 mmol) of the azide intermediate (obtained from Step 1) in 75 mL of ethanol was added 0.10 g of 10% palladium on carbon and the mixture shaken under 49 psi of hydrogen at ambient temperature for 3.5

hours. The reaction was filtered through celite and concentrated in vacuo to give 0.62 g (86% RPHPLC purity, ca. 84%) of pentyl amine intermediate as an off-white foam. The sample was used without further purification: mp 70-85 °C; ^1H NMR (CDCl_3) δ 0.86-0.96 (m, 6H), 1.06-1.75 (m, 15H), 1.79-1.93 (m, 4H), 2.15-2.28 (m, 1H), 2.82 (s, 6H), 2.96-3.20 (m, 4H), 3.99 (t, J = 6.0 Hz, 2H), 4.04-4.14 (m, 1H), 5.49 (s, 1H), 6.00 (d, J = 1.5 Hz, 1H), 6.51 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H). MS (ES, M+H) m/e 545.

[1257] Step 3: Preparation of guanidine

[1258] To a stirred solution of 258 mg (0.474 mmol) of pentyl amino intermediate (obtained from Step 2) and 81 mg (0.551 mmol) of 1H-pyrazole-1-carboxamide hydrochloride in 1.5 mL of DMF was added 71 mg (0.551 mmol) of diisopropylethylamine. The reaction was stirred at ambient temperature for 16 hours. Purification by reversed phase chromatography (Waters-Delta prep) using 60% water/acetonitrile afforded 120 mg (43%) of the desired title compound as colorless foamy solid: mp 67.0-72.5 °C; ^1H NMR (CDCl_3) δ 0.89-0.93 (m, 6H), 1.05-1.17 (m, 1H), 1.26-1.90 (m, 16H), 2.07-2.24 (m, 1H), 2.81 (s, 6H), 2.99-3.19 (m, 4H), 3.98 (br s, 2H), 4.12 (s, 1H), 5.46 (s, 1H), 6.01 (d, J = 2.1 Hz, 1H), 6.51 (dd, J = 2.1, 8.0 Hz, 1H), 6.92 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.89 (d, J = 8.7 Hz, 1H). HRMS. Calc'd for $\text{C}_{32}\text{H}_{50}\text{N}_4\text{O}_4\text{S}$: 586.3552. Found(M+H): 587.3620.

[1259] Example 1423



[1260] (4R-cis)-N-[5-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]pentyl]glycine

[1261] Step 1: Preparation of pentyl azide intermediate

[1262] To a solution of pentyl bromide intermediate (400 mg, 0.657 mmol, obtained from Example 1420, Step 1) in dimethyl sulfoxide (20 mL) was added sodium azide (47 mg, 0.723 mmol, 1.1 eq), and the resulting clear solution was stirred at 23°C for 16h. The reaction solution was diluted with 100 mL ethyl acetate, then washed with water (2x 100 mL) and brine (1x 100 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo to give 390 mg (quantitative) of pentyl azide intermediate as a yellow oil: ¹H NMR (CDCl₃) δ 0.82-0.90 (m, 7H), 1.05-1.56 (m, 12H), 1.59-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, *J* = 8.3 Hz, 1H), 2.82 (s, 6H), 3.08 (q, 2H), 3.44 (t, *J* = 7.7 Hz, 2H), 3.99 (t, *J* = 7.7 Hz, 2H), 4.91 (br s, 1H), 5.47 (s, 1H), 6.13 (d, *J* = 7.58 Hz, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 7.14 (ABq, 4H), 7.91 (d, *J* = 7.8 Hz, 1H).

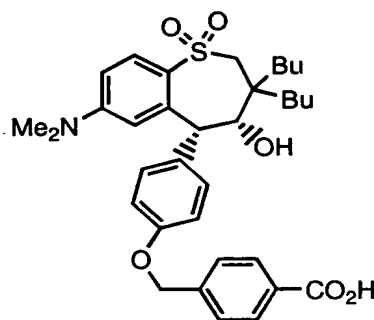
[1263] Step 2: Preparation of amino ester intermediate

[1264] A suspension of pentyl azide intermediate (390 mg, 0.684 mmol, obtained from Step 1) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 4.5 hours. The ethanolic suspension was filtered through celite and concentrated in vacuo to give a yellow oil. The oil was immediately diluted with acetonitrile (15 mL), followed by the addition of triethylamine (0.156 g, 1.54 mmol, 2.25 eq) and bromo acetic acid benzyl ester (0.212 g, 0.925 mmol, 1.35 eq). The reaction was stirred at 23°C for 48 hours. The reaction was concentrated in vacuo, and the residue was dissolved in ethyl acetate (20 mL) and washed with water (2x 20 mL) and brine (1x 20 mL). The organic layer was dried (MgSO₄) and dried in vacuo to give 420 mg (89%) of the amino ester intermediate as a yellow oil: ¹H NMR (CDCl₃) δ 0.82-0.90 (m, 6H), 1.05-1.56 (m, 14H), 1.58-1.71 (m, 3H), 1.78-2.01 (m, 4H), 2.20 (t, *J* = 8.3 Hz, 1H), 2.75 (d, *J* = 7.83 Hz, 1H), 2.795 (s, 6H), 3.08 (q, 2H), 3.68-3.85 (m, 2H), 3.87-4.04 (m, 2H), 4.09 (s, 1H), 5.147 (s, 1H), 5.46 (s, 1H), 5.98 (d, *J* = 7.58, 1H), 6.50 (dd, 1H), 6.85-6.87 (m, 2H), 7.28-7.45 (m, 5H), 7.89 (d, *J* = 8.0 Hz, 1H). MS (ES) *m/e* 693.

[1265] Step 3: Preparation of acid

[1266] A suspension of benzyl ester intermediate (0.420g, 0.61 mmol, obtained from Step 2) and 100 mg of palladium on carbon in ethanol (15 mL) was agitated under an atmosphere of hydrogen gas (48 psi) for 16h. The suspension was filtered through celite, and concentrated in vacuo to give 0.330g of a yellow semi-solid. The material was triturated with diethyl ether and the remaining semi-solid was dried in vacuo to give 0.19 g (52%) of the desired title compound as a yellow semi solid: ^1H NMR (CDCl_3) δ 0.86 (br s, 7H), 1.0-1.72 (m, 18H), 1.79 (br s, 2H), 1.98 (s, 2H), 2.09-2.24 (m, 2H), 2.78 (s, 6H), 2.99 (q, 2H), 3.96 (bs, 2H), 4.08 (s, 1H), 5.46 (s, 1H), 5.97 (s, 1H), 6.40-6.49 (m, 1H), 7.14 (ABq, 4H), 7.85 (t, $J = 7.93$ Hz, 1H). MS (ES) m/e 603.

[1267] Example 1424



[1268] (4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]benzoic acid

[1269] Step 1: Preparation of benzoate intermediate

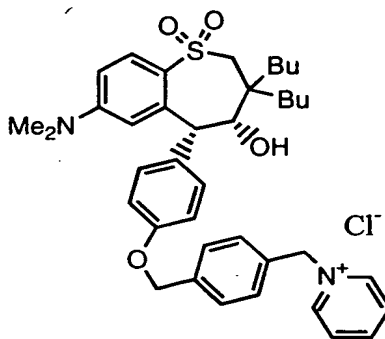
[1270] To a solution of 0.53 g (1.15 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzo-thiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 10 mL dimethylformamide was added 35 mg (1.39 mmol) of 95% sodium hydride and stirred for 10 minutes. To the reaction mixture was added 525 mg (2.29 mmol) methyl 4-(bromomethyl)benzoate and stirred for 16 hours. Water was added to the reaction mixture, extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.51 g (73%) of the benzoate intermediate: ^1H

NMR (CDCl₃) δ 0.86-0.96 (m, 6H), 1.14-1.47 (m, 10H), 1.60-1.64 (m, 1H), 2.20-2.23 (m, 1H), 2.80 (s, 6H), 2.99 (d, J = 15.1 Hz, 1H), 3.15 (t, J = 15.1 Hz, 1H), 3.92 (s, 3H), 4.09-4.15 (m, 1H), 5.17 (s, 2H), 5.49 (s, 1H), 5.94 (d, J = 2.2 Hz, 1H), 6.50 (dd, J = 8.9, 2.6 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.9 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H).

[1271] Step 2: Preparation of acid

[1272] A solution of 0.51 g (0.84 mmol) of the benzoate intermediate (obtained from Step 1) and 325 mg (2.53 mmol) of KOSi(CH₃)₃ (Aldrich) in 16 mL THF was stirred for 3.5 hours. The THF was evaporated, water added, extracted with ethyl acetate, dried over magnesium sulfate, filtered and the solvent evaporated to afford 0.30 g (60%) of the desired title compound as a white solid: mp 156 - 159 °C; ¹H NMR (CDCl₃) δ 0.89-0.94 (m, 6H), 1.24-1.43 (m, 10H), 1.62-1.66 (m, 1H), 2.20-2.24 (m, 1H), 2.84 (s, 6H), 3.02 (d, J = 15.1 Hz, 1H), 3.17 (d, J = 15.1 Hz, 1H), 4.14 (s, 1H), 5.20 (s, 2H), 5.50 (s, 1H), 6.16 (s, 1H), 6.71 (d, J = 9.1 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.95 (d, J = 8.9 Hz, 1H), 8.13 (d, J = 8.1 Hz, 2H). HRMS. Calc'd for C₃₄H₄₄NO₆S: 594.2889. Found: 594.2913.

[1273] Example 1425



[1274] (4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]pyridinium chloride

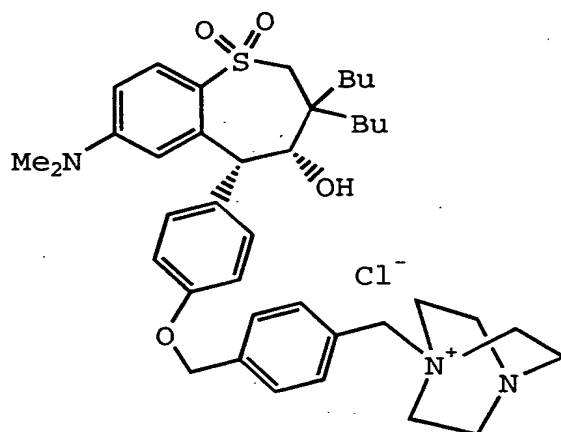
[1275] Step 1: Preparation of chlorobenzyl intermediate

[1276] A solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (5.0 g, 10.9 mmol, obtained from Example 1402, Step 10) in acetone (100 mL) at 25°C under N₂ was treated with powdered K₂CO₃ (2.3 g, 16.3 mmol, 1.5 eq.) and α,α' -dichloro-*p*-xylene (6.7 g, 38.1 mmol, 3.5 eq.) and the resulting solution was stirred at 65°C for 48 hours. The reaction mixture was cooled to 25°C and concentrated to 1/5 of original volume. The residue was dissolved in EtOAc (150 mL) and washed with water (2 x 150 mL). The aqueous layer was extracted with EtOAc (2 x 150 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 150 mL). The combined extracts were dried (MgSO₄) and concentrated in vacuo to provide a yellow oil. Purification by flash chromatography (5.4 x 45 cm silica, 25-40% EtOAc/hexane) afforded the chlorobenzyl intermediate (4.7 g, 72%) as a white foam: ¹H NMR (CDCl₃) δ 0.89-0.94 (m, 6H), 1.12-1.48 (br m, 10H), 1.63 (m, 1H), 2.22 (m, 1H), 2.81 (s, 6H), 3.05 (ABq, J = 15.1 Hz, J = 50.0 Hz, 2H), 4.11 (d, J = 8.1 Hz, 1H), 4.60 (s, 2H), 5.11 (s, 2H), 5.48 (s, 1H), 5.96 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.9, 2.6 Hz, 1H), 7.00 (d, J = 8.9 Hz, 2H), 7.36-7.47 (m, 5H), 7.85 (d, J = 8.9 Hz, 1H).

[1277] Step 2: Preparation of quaternary salt

[1278] A solution of the chlorobenzyl intermediate (1.0 g, 1.7 mmol, obtained from Step 1) in acetonitrile (5 mL) at 25°C under N₂ was treated with pyridine (5 mL) and stirred at 35°C for 36 hours. The pale amber solution was cooled to 25°C and concentrated in vacuo to give the desired title compound (1.08 g, 96%) as a yellow solid: mp 154-156 °C; ¹H NMR (CDCl₃) δ 0.83 (m, 6H), 1.06-1.44 (br m, 10H), 1.60 (m, 1H), 2.13 (m, 1H), 2.71 (s, 6H), 3.02 (ABq, J = 15.1 Hz, J = 28.4 Hz, 2H), 4.09 (s, 1H), 5.00 (s, 2H), 5.38 (s, 1H), 5.91 (d, J = 2.4 Hz, 1H), 6.26 (s, 2H), 6.41 (dd, J = 8.9, 2.4 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 7.26 (m, 1H), 7.40 (d, J = 7.7 Hz, 4H), 7.73 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.93 (t, J = 6.8 Hz, 1H), 8.34 (t, J = 7.7 Hz, 1H), 8.58 (br s, 1H), 9.69 (d, J = 5.8 Hz, 2H); HRMS. Calc'd for C₃₉H₄₉N₂O₄S: 641.3413. Found: 641.3425.

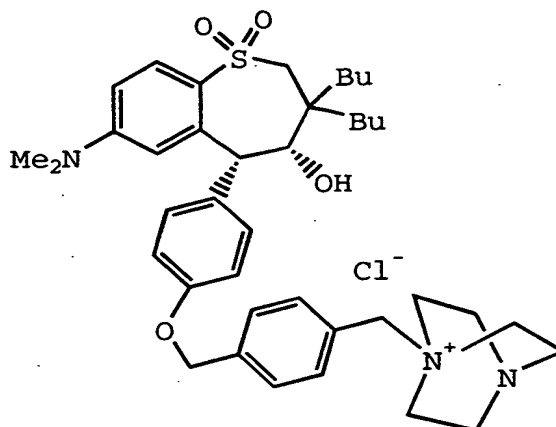
[1279] Example 1426



[1280] (4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride

[1281] Under N₂, a solution of 8.7 g (14.5 mmol) of the chlorobenzyl intermediate (obtained from a procedure similar to the one outlined in Example 1425, Step 1) in 60 mL of acetonitrile was added dropwise over a 30 min period to a solution of 2.9 g (26.2 mmol) of diazabicyclo[2.2.2]octane (DABCO) in 40 mL of acetonitrile at 35°C; during the addition, a colorless precipitate was formed. The slurry was stirred at 35°C for an additional 2 h. The product was collected and washed with 1 L of acetonitrile to give 9.6 g (93%) the title compound as a colorless crystalline solid: mp 223-230°C (decomposed); ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, *J* = 15.1 Hz, *J* = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, *J* = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for C₄₀H₅₆N₃O₄S: 674.3992. Found: 674.4005.

[1282] Example 1426a



[1283] **(4R-cis)-1-[[4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy)methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride**

[1284] A solution of the chlorobenzyl intermediate (4.6 g, 7.7 mmol, obtained from Example 1425, Step 1) in acetonitrile (100 mL) at 25°C under N₂ was treated with diazabicyclo[2.2.2]-octane (DABCO, 0.95 g, 8.5 mmol, 1.1 eq.) and stirred at 35°C for 2 hours, during which time a white solid precipitated out. The white solid was collected, washed with CH₃CN and recrystallized from CH₃OH/Et₂O to give the title compound (4.95 g, 91%) as a white solid: mp 223-230°C (decomposed); ¹H NMR (CDCl₃) δ 0.89 (m, 6H), 1.27-1.52 (br m, 10H), 1.63 (m, 1H), 2.20 (m, 1H), 2.81 (s, 6H), 3.06 (ABq, *J* = 15.1 Hz, *J* = 43.3 Hz, 2H), 3.16 (s, 6H), 3.76 (s, 6H), 4.11 (d, *J* = 7.7 Hz, 1H), 5.09 (s, 2H), 5.14 (s, 2H), 5.48 (s, 1H), 5.96 (s, 1H), 6.49 (d, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.26 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 1H); HRMS. Calc'd for C₄₀H₅₆N₃O₄S: 674.3992. Found: 674.4005.

Chemical structure of compound 10: A 1,3-dioxane derivative with a sulfone group, a dimethylaminophenyl group, a hydroxyl group, and a 4-(benzyloxy)phenyl group. The 4-(benzyloxy)phenyl group is further substituted with a 2,2'-bipyridine-5,5'-dicarboxylic acid moiety.

[1287] Step 1: Preparation of chlorobenzyl intermediate

[1289] Step 2: Preparation of amino diester

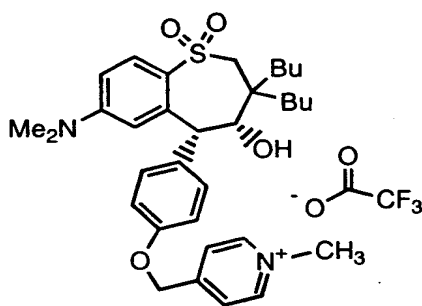
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purified by column chromatography to give amino diester intermediate: ^1H NMR (CDCl_3) δ 0.90 (q, 6H), 1.05-1.65 (m, 17H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.55 (s, 4H), 3.95 (s, 2H), 4.1-4.2 (m, 5H), 5.05 (s, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (s, 6H), 7.8 (d, 1H).

[1291] Step 3: Preparation of amino diacid

[1292] A solution of 0.863 g (1.15 mmol) of dibenzyl ester (obtained from Step 2) and 0.232 g (5.52 mmol) of LiOH in 30 mL of THF and 30 mL of water was stirred at 40°C under N_2 for 4 hours. The reaction mixture was diluted with ether and washed with 1% HCl. The aqueous layer was extracted twice with ether, and the combined extracts were washed with brine, dried over MgSO_4 , and concentrated in vacuo to give the desired title compound as a solid: mp 175 °C; ^1H NMR (THF- d_8) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.22 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.5 (s, 4H), 3.9 (s, 2H), 4.1 (d, 1H), 5.1 (s, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.5 (d, 1H), 7.0 (d, 2H), 7.4 (m, 6H), 7.78 (d, 1H). HRMS. Calc'd for $\text{C}_{38}\text{H}_{50}\text{N}_2\text{O}_8\text{S}$: 695.3366. Found: 695.3359. Anal. Calc'd for $\text{C}_{38}\text{H}_{50}\text{N}_2\text{O}_8\text{S}$: C, 65.68; H, 7.25; N, 4.03; S, 4.61. Found: C, 64.95; H, 7.32; N, 3.94; S, 4.62.

[1293] Example 1428



[1294] (4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium salt with trifluoroacetic acid (1:1)

[1295] Step 1: Preparation of picolyl intermediate

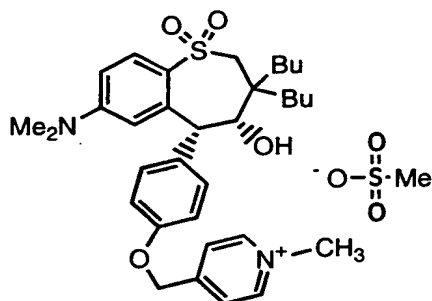
[1296] To a stirred solution of 12.0 g (26.1 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetra-hydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 200 mL of DMF was added 1.4 g (60% oil dispersion, 35 mmol) of sodium hydride and the reaction stirred at ambient temperature for one hour. 5.99 g (36.5 mmol) of 4-picolyl chloride hydrochloride was treated with cold saturated NaHCO₃ solution and extracted with diethyl ether. The ethereal extracts were washed with brine, dried over MgSO₄, and filtered. The reaction was cooled in an ice bath and the solution of 4-picolyl chloride in diethyl ether was added. The reaction was stirred at ambient temperature for 17 hours. The reaction was quenched with 25 mL of saturated NH₄Cl, diluted with 600 mL ethyl acetate washed with 4X250 mL water, brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (Waters-prep 500) using 60% ethyl acetate/hexanes afforded 11.05 g (77%) of the picoliny intermediate as a colorless solid: mp 95-98 °C; ¹H NMR (CDCl₃) δ 0.86-0.96 (m, 6H), 1.02-1.52 (m, 10H), 1.58-1.70 (m, 1H), 2.16-2.29 (m, 1H), 2.81 (s, 6H), 3.07 (AB_q, J_{AB} = 15.3, 49.6 Hz, 2H), 4.10 (d, J = 7.5 Hz, 1H), 5.15 (s, 2H), 5.50 (s, 1H), 5.94 (d, J = 2.7 Hz, 1H), 6.51 (dd, J = 2.4, 8.7 Hz, 1H), 7.00 (d, J = 9.0 Hz, 2H), 7.39 (d, 6.0 Hz, 2H), 7.44 (s, J = 8.7 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H), 8.63 (dd, J = 1.6, 4.8 Hz, 2H).

[1297] Step 2: Preparation of quaternary salt

[1298] To a stirred solution of 0.41 g (0.74 mmol) of picoliny intermediate (obtained from Step 1) in 10 mL of acetonitrile and 3 mL of dichloromethane was added 137 mg (0.97 mmol) of iodomethane. The reaction was stirred at ambient temperature for 16 hours, then concentrated under a nitrogen stream. Purification by reversed phase chromatography (Waters-Delta prep) using 60-55% water/acetonitrile afforded 0.304 g (60%) of the desired title compound as a colorless solid: mp 96-99 °C; ¹H NMR (CDCl₃) δ 0.85-0.95 (m, 6H), 1.03-1.52 (m, 10H), 1.57-1.70 (m, 1H), 2.12-2.27 (m, 1H), 2.84 (s, 6H), 3.09 (AB_q, J_{AB} = 15.0, 27.9 Hz, 2H), 4.11 (s, 1H), 4.46 (s, 3H), 5.37 (s, 2H), 5.50 (s, 1H), 6.07 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 2.5, 8.7 Hz, 1H), 7.02 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 6.3

Hz, 2H), 8.80 (d, $J = 6.6$ Hz, 2H). HRMS Calc'd for $C_{33}H_{45}N_2O_4S$: 565.3100. Found: 565.3125.

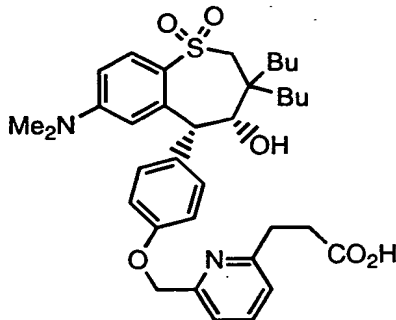
[1299] Example 1429



[1300] (4R-cis)-4-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-1-methylpyridinium, methanesulfonate (salt)

[1301] To a stirred solution of 6.5 g (11.8 mmol) of picolyl intermediate (obtained from Example 1428, Step 1) in 140 mL of acetonitrile heated at 70°C was added 1.56 g (14.6 mmol) methanesulfonic acid methyl ester. Heating was continued at 70°C for 15 hours. The reaction was cooled and diluted with 50 mL of ethyl acetate. The solid was collected by vacuum filtration to give 6.14 g (79%). The filtrate was concentrated in vacuo and the residue crystallized from hot acetonitrile to give 1.09 g (14%). A total of 7.23 g (93%) of the desired title compound was obtained as an off-white solid: mp 232-233.5 °C; 1H NMR ($CDCl_3$) δ 0.66-0.76 (m, 6H), 0.85-0.95 (m, 1H), 0.95-1.35 (m, 9H), 1.42- 1.54 (m, 1H), 1.95-2.22 (m, 1H), 2.50 (s, 1H), 2.56 (s, 3H), 2.63 (s, 6H), 2.91 (AB_q, $J = 16.5, 24.0$ Hz, 2H), 3.88 (s, 1H), 4.40 (s, 3H), 5.21 (s, 3H), 5.78 (d, $J = 2.4$ Hz, 1H), 6.31 (dd, $J = 2.5, 8.7$ Hz, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 8.7$ Hz, 1H), 8.0 (d, $J = 6.6$ Hz, 2H), 9.02 (d, $J = 6.6$ Hz, 2H). HRMS Calc'd for $C_{33}H_{45}N_2O_4S$: 565.3100. Found: 656.3087. Anal. Calc'd for $C_{34}H_{48}N_2O_7S_2$: C, 61.79; H, 7.32; N, 4.24; S, 9.70. Found: C, 61.38, H, 7.47; N, 4.22; S, 9.95.

[1302] Example 1430



[1303] (4R-cis)-6-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinepropanoic acid

[1304] **Step 1: Preparation of picoliny chloride intermediate**

[1305] To a solution of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (1g, 2.1 mmol, obtained from Example 1402, Step 10) in acetone (50 mL) was added anhydrous K_2CO_3 (0.45g, 3.2 mmol), tetrabutylammonium iodide (0.1g, 0.2 mmol) and 2,6-bis(chloromethyl)pyridine (1.2g, 10.8 mmol). The flask was equipped with nitrogen gas adapter and magnetic stirrer. The reaction was heated to reflux for overnight. After 18 hours, the reaction was diluted with ether and washed with water and brine (30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Chromatographic purification through silica gel, eluting with 25% EtOAc/Hexane gave 0.75 g (55%) of the picolyl chloride intermediate as an oil (0.70g, 55%): 1H NMR ($CDCl_3$) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 4.10 (d, 2H), 4.65 (s, 2H), 5.20 (s, 2H), 5.45 (s, 1H), 5.95 (s, 1H), 6.50 (d, 1H), 7.0 (d, 2H), 7.35-7.50 (m, 4H), 7.70-7.85 (m, 2H).

[1306] **Step 2: Preparation of pyridinyl malonate intermediate**

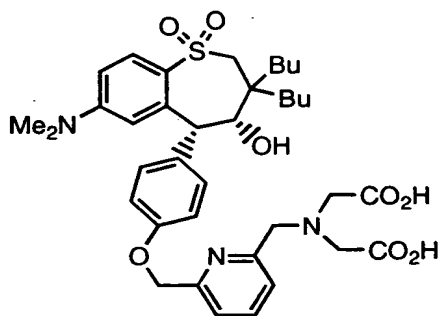
[1307] Dibenzyl malonate (1.42g, 5.01 mmol) in DMF (20.0 mL) and sodium hydride (0.13g, 3.3 mmol) were placed in a dry three-neck flask. The flask was equipped with nitrogen gas adapter and magnetic stirrer. The picolyl chloride intermediate (1g, 1.67 mmol) was added and heated at 90°C for overnight. The

reaction was cooled and extracted with 5% HCl with methylene chloride and washed with water (25 mL), and brine (50 mL). The organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by C-18 reversed phase column eluting with 50% acetonitrile/water and gave pyridinyl malonate intermediate as a white foamy solid (1g, 71%): ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.22 (d, 2H), 4.05 (d, 1H), 4.16 (t, 1H), 5.02(s, 2H), 5.08 (s, 4H), 5.44 (s, 1H), 5.97 (s, 1H), 6.96-7.10 (m, 3H), 7.20-7.32 (m, 12H), 7.5 (t, 1H), 7.9 (d, 1H).

[1308] Step 3: Preparation of pyridinyl acid

[1309] The pyridinyl malonate intermediate (0.6g, 0.7 mmol, obtained from Step 2), THF/water (25.0 mL, 1:1) and lithium hydroxide monohydrate (0.14 g, 3.4 mmol) were placed in a 100 mL round-bottom flask. The reaction was stirred at ambient temperature overnight. After 18 hours, the reaction was extracted with 1% HCl and ether and then washed with water (20 mL) and brine (30 mL). The organic layers were dried over MgSO₄, filtered and concentrated in vacuo gave the desired title compound as a white solid (0.44g, 90%): mp 105-107 °C; ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H), 3.05 (m, 2H), 3.10 (ABq, 2H), 3.22 (m, 2H), 4.05 (s, 1H), 5.30 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for C₃₅H₄₆N₂O₆S: 623.3155. Found: 623.3188.

[1310] Example 1431



[1311] (4R-cis)-N-(Carboxymethyl)-N-[[[6-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-2-pyridinyl]methyl]glycine

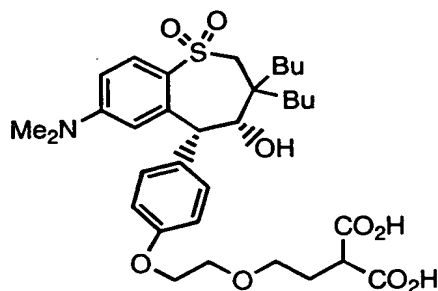
[1312] Step 1: Preparation of pyridinyl diester intermediate

[1313] A mixture of diethyl aminodiacetate (8g, 68 mmol) and sodium carbonate (0.63g, 5.9 mmol) was treated with picolyl chloride intermediate (0.72g, 1.2 mmol, obtained from Example 1430, Step 1), and stirred at 160°C for three hours. The reaction was cooled and diluted with ether and washed with 1% HCl, water (25 mL), and brine (50 mL). The combined extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by distillation in the Kugelrohr to give pyridinyl diester intermediate as a yellowish foamy solid (0.72g, 80%): ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 16H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H) 3.05 (ABq, 2H), 3.70 (s, 4H), 4.2-4.4 (m, 6H), 5.30 (s, 2H), 5.56 (s, 1H), 6.02 (s, 1H), 6.60 (d, 1H), 7.10 (d, 2H), 7.50 (m, 3H), 7.61 (d, 1H), 7.80 (t, 1H), 7.95 (d, 1H). HRMS. Calc'd for C₄₁H₅₇N₃O₈S: 752.3945. Found: 752.3948.

[1314] Step 2: Preparation of pyridinyl diacid

[1315] A mixture of pyridine-aminodiacetate intermediate (0.7g, 0.93 mmol, obtained from Step 1), and lithium hydroxide monohydrate (0.18 g, 4.5 mmol) in THF/ water (25.0 mL, 1:1) was stirred at 40°C overnight (18 hours). The reaction mixture was diluted with ether and washed with 1% HCl, water (20 mL), and brine (30 mL). The organic layers were dried over MgSO₄, filtered and concentrated in vacuo to give the desired title compound as a white solid (0.44g, 90%): mp 153-155 °C; ¹H NMR (CDCl₃) δ 0.84-0.95 (m, 6H), 1.02-1.5 (m, 10H), 1.56-1.66 (m, 1H), 2.14-2.24 (m, 1H), 2.80 (s, 6H), 3.10 (ABq, 2H), 3.90 (m, 3H), 4.05 (s, 1H), 4.40 (s, 2H), 5.20 (s, 2H), 5.50 (s, 1H), 5.97 (s, 1H), 6.50 (d, 1H), 7.02 (d, 2H), 7.3 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.8-7.9 (m, 2H). HRMS. Calc'd for C₃₇H₄₉N₃O₈S: 696.3319. Found: 696.3331.

[1316] Example 1432



[1317] (4S-cis)-[2-[2-[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]ethoxy]ethyl]propanedioic acid

[1318] **Step 1: Preparation of bromoethyl ether intermediate**

[1319] To a stirred solution of 0.192 g (4.785 mmol, 60% disp) of NaH in 28 mL of DMF was added 2.0 g (4.35 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10), and the resulting solution was stirred at ambient temperature for 30 min. To the solution was added 13.2 g (54.38 mmol) of bis(2-bromoethyl)ether, and stirring was continued at ambient temperature under N₂ overnight. DMF was removed in vacuo and the residue was extracted with ethyl acetate and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give bromoethyl ether intermediate: ¹H NMR (CDCl₃) δ 0.90 (q, 6h), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.5 (t, 2H), 3.9 (m, 4H), 4.1 (d, 1H), 4.2 (d, 2H), 5.42 (s, 1H), 5.95 (s, 1H), 6.5 (d, 1H), 6.95 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

[1320] **Step 2: Preparation of diester intermediate**

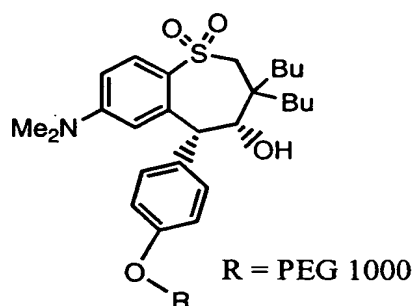
[1321] To a mixture of 94 mg (2.34 mmol, 60% disp) of NaH in 45 mL of THF and 15 mL of DMF at 0°C was added 1.33 g (4.68 mmol) of dibenzyl malonate (Aldrich), and the resulting solution was stirred at ambient temperature for 15 min, followed by the addition of 0.95 g (1.56 mmol) of bromoethyl ether intermediate (obtained from Step 1). The mixture was stirred under N₂ at 80°C

overnight. Solvent was removed in vacuo and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO_4 , and the concentrated residue was purified by column chromatography to give the diester intermediate: ^1H NMR (CDCl_3) δ 0.90 (q, 6H), 1.05-1.65 (m, 11H), 2.2-2.3 (m, 3H), 2.8 (s, 6H), 3.0 (q, 2H), 3.6 (t, 2H), 3.7 (m, 3H), 4.1 (m, 3H), 5.1 (s, 4H), 5.42 (s, 1H), 5.9 (s, 1H), 6.5 (d, 1H), 6.9 (d, 2H), 7.3 (m, 10H), 7.4 (d, 2H), 7.9 (d, 1H).

[1322] Step 3: Preparation of diacid

[1323] A suspension of 0.761 g (0.935 mmol) of the diester intermediate (obtained from Step 2) and 35 mg of 10% Pd/C in 25 mL of ethanol and 5 mL of THF was agitated at ambient temperature under 20 psi of hydrogen gas for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to give the desired title compound as a solid: mp 119.5 °C; ^1H NMR (THF-d_8) 0.95 (q, 6H), 1.05-1.65 (m, 11H), 2.1 (q, 2H), 2.25 (t, 1H), 2.8 (s, 6H), 3.0 (t, 2H), 3.47 (q, 2H), 3.58 (s, 1H), 3.78 (t, 2H), 4.08 (d, 1H), 4.15 (t, 2H), 5.4 (s, 1H), 6.05 (s, 1H), 6.55 (d, 1H), 6.98 (d, 2H), 7.42 (d, 2H), 7.8 (d, 1H). HRMS. Calc'd for $\text{C}_{33}\text{H}_{47}\text{NO}_9\text{S}$: 632.2893. Found: 632.2882. Anal. Calc'd for $\text{C}_{33}\text{H}_{47}\text{NO}_9\text{S}$: C, 62.54; H, 7.47; N, 2.21; S, 5.06. Found: C, 61.75; H, 7.56; N, 2.13; S, 4.92.

[1324] Example 1433



[1325] (4R-cis)-a-[[4-[3,3-Dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]-w-methoxypoly(oxy-1,2-ethanediyl)

[1326] Step 1: Preparation of monomethyl PEG mesylate intermediate

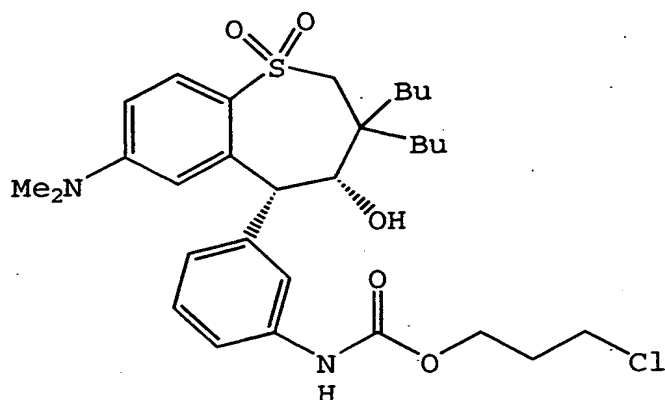
[1327] To a solution of 20 g of monomethyl ether PEG in 100 mL of methylene chloride was added 2.2 g (22 mmol) of triethyl amine, and to the resulting solution at 0°C was added dropwise 2.5 g (22 mmol) of methanesulfonyl chloride. The resulting solution was stirred overnight at ambient temperature, and the triethyl amine hydrochloride was filtered off to give the monomethyl PEG mesylate intermediate which was used in the next Step without further purification and characterization.

[1328] Step 2: Preparation of polyethylene-linked benzothiepine

[1329] A mixture of 38 mg (1.52 mmol 95%) of NaH and 0.7 g (1.52 mmol) of 5-(4'-hydroxyphenyl)-7-(dimethylamino)tetrahydrobenzothiepine-1,1-dioxide (obtained from Example 1402, Step 10) in 5.5 mL of DMF was stirred at ambient temperature under N₂ for 30 min. To the solution was added 0.55 g (0.51 mmol) of the mesylate PEG intermediate (obtained from Step 1) in 5.5 mL of DMF, and the resulting solution was stirred overnight under N₂ at 50 °C. DMF was removed in vacuo and the residue was extracted with methylene chloride and washed with brine. The extract was dried over MgSO₄, and the concentrated residue was purified by column chromatography to give the desired title compound as an oil: ¹H NMR (CDCl₃) δ 0.9 (q, 6h), 1.05-1.65 (m, 11H), 2.2 (t, 1H), 2.8 (s, 6H), 3.0 (q, 2H), 3.4 (s, 4H), 3.5-3.85 (m, 95H), 4.1 (s, 1H), 4.15 (t, 2H), 5.5 (s, 1H), 6.05 (s, 1H), 6.6 (d, 1H), 6.9 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H).

[1330] Example 1434

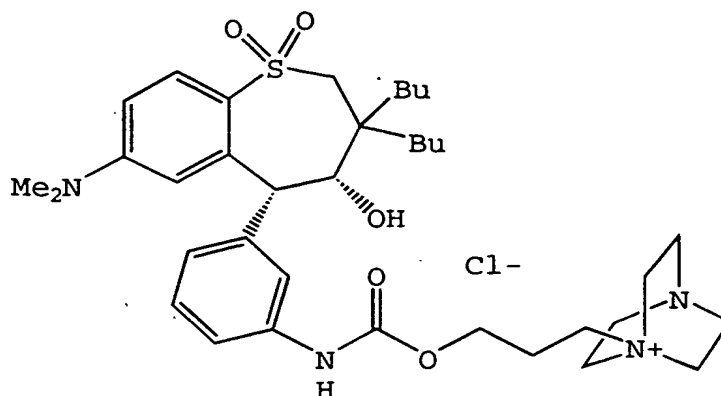
[1331] Preparation of:



[1332] The 3-aminobenzothiepine prepared in Step 5 of Example 1398 (0.380g, 0.828 mmol), sodium hydroxide (0.35 mL, 0.875 mmol, 10% in H₂O) and toluene (0.50 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂, equipped with magnetic stirrer, and cooled to 0 °C. A solution of 3-chloropropyl chloroformate (1.440g, 1.10 mmol, 12% in CH₂Cl₂/ THF) was added. After 3.5 hrs, toluene (3.0 mL) was added, and the mixture was washed with H₂O (2x4 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20% EtOAc/hexane and concentrated *in vacuo* gave a white solid (0.269g, 56%). ¹H NMR (CDCl₃) δ 0.87-0.93 (m, 6H), 1.05-1.70 (m, 11H), 2.14 (t, J = 6.3 Hz, 2H), 2.15-2.25 (m, 1H), 2.81 (s, 6H), 3.07 (ABq, 2H), 3.64 (t, J = 6.3 Hz, 2H), 4.11 (d, J = 7.5 Hz, 1H), 4.33 (t, J = 6.0 Hz, 2H), 5.50 (s, 1H), 5.99 (d, J = 2.4 Hz, 1H), 6.51 (dd, J = 9.0, 2.7 Hz, 1H), 6.65 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.34-7.39 (m, 2H), 7.54 (d, J = 7.2 Hz, 1H), 7.89 (d, 8.7 Hz, 1H). HRMS (M + H). Calc'd for C₃₀H₄₄N₂O₅SCl: 579.2659. Found: 579.2691.

[1333] Example 1435

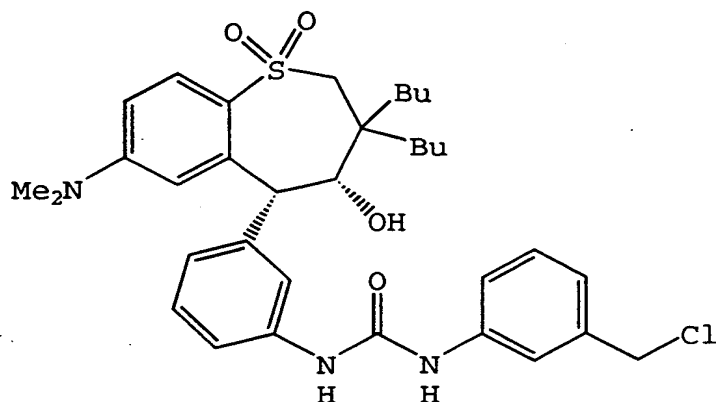
[1334] Preparation of:



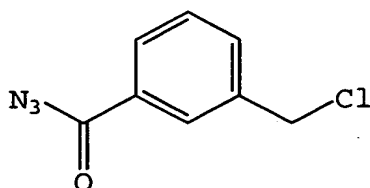
[1335] 1,4-Diazabicyclo(2.2.2)octane (0.0785g, 0.700 mmol) and acetonitrile (1.0 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂, equipped with magnetic stirrer, and heated to 37 °C. A solution of the product of Example 1434 (0.250g, 0.432 mmol) in acetonitrile (2.50 mL) was added. After 2.5 hrs, 1,4-diazabicyclo(2.2.2)octane (0.0200g, 0.178 mmol) was added. After 64 hrs, 1,4-diazabicyclo(2.2.2)octane (0.0490g, 0.437 mmol) was added. After 24 hrs, the reaction mixture was cooled to R.T. and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (2.0 mL) and precipitated with ethyl ether (10.0 mL). The precipitate was filtered to yield a white solid. This trituration method was repeated, followed by concentrated *in vacuo* to give a white solid (0.185g, 62%). mp 218.0-225.0 °C; ¹H NMR (CD₃OD) δ 0.90 (m, 6H), 1.05-1.55 (m, 10H), 1.16 (t, J = 6.6 Hz, 2H), 1.78 (m, 1H), 2.12 (m, 3H), 2.76 (s, 6H), 3.10 (m, 2H), 3.17 (t, J = 7.2 Hz, 6H), 3.30-3.50 (m, 8H), 4.10 (s, 1H), 4.21 (t, J = 5.4 Hz, 2H), 5.31 (s, 1H), 6.10 (s, 1H), 6.55 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 6.9 Hz, 1H), 7.33-7.42 (m, 2H), 7.56 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H). HRMS. Calc'd for C₃₆H₅₅N₄O₅SCl: 655.3893. Found: 655.3880.

[1336] Example 1436

[1337] Preparation of:



[1338] Step 1. Preparation of:



[1339] 3-Chloromethylbenzoyl chloride (2.25 mL/15.8 mmol) and acetone (8.0 mL) were combined in a 25 mL round-bottom flask. The reaction flask was cooled to 0°C, and an aqueous solution of sodium azide (1.56g in 5.50 mL/24.0 mmol) was added. After 1.5 hrs, the reaction mixture was poured into ice water (80.0 mL), extracted with ethyl ether (2x25 mL), dried (MgSO₄), and concentrated *in vacuo* to give a colorless oil (2.660g, 86%). ¹H NMR (CDCl₃) δ 4.62 (s, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H).

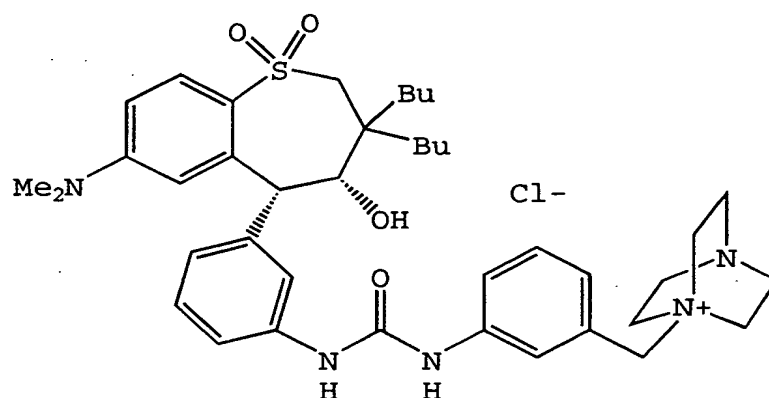
[1340] Step 2.

[1341] 3-Chloromethylbenzoyl azide (0.142g, 0.726 mmol) and toluene (2.0 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N₂, equipped with magnetic stirrer, and heated to 110 °C. After 2 hrs, the reaction mixture was cooled to R.T, and the 3-aminobenzothiepine prepared in Step 5 of Example 1398 (0.365g, 0.796 mmol) was added. After 2.25 hrs, the mixture was heated to 50 °C. After 0.75 hrs, 3-chloromethylbenzoyl azide (0.025g, 0.128 mmol) was added, and the reaction mixture was heated to reflux. After 0.5 hrs, the reaction mixture was cooled to R.T. and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20-

30% EtOAc/hexane and concentrated *in vacuo* gave a white foamy solid (0.309g, 62%). ^1H NMR (CDCl_3) δ 0.71 (t, J = 5.4 Hz, 3H), 0.88 (t, J = 6.3 Hz, 3H), 1.03-1.60 (m, 11H), 1.85 (d, 6.3 Hz, 1H), 2.27 (m, 1H), 2.76 (s, 6H), 3.15 (t, 2H), 4.17 (d, J = 6.6 Hz, 1H), 4.48 (s, 2H), 5.42 (s, 1H), 6.07 (s, 1H), 6.99 (d, J = 7.5 Hz), 7.18-7.26 (m, 2H), 7.30-7.41 (m, 3H), 7.63 (s, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.96 (s, 1H), 8.17 (s, 1H). HRMS ($M + \text{Li}$). Calculated for $\text{C}_{34}\text{H}_{44}\text{N}_3\text{O}_4\text{SClLi}$: 632.2901. Found: 632.2889.

[1342] Example 1437

[1343] Preparation of:

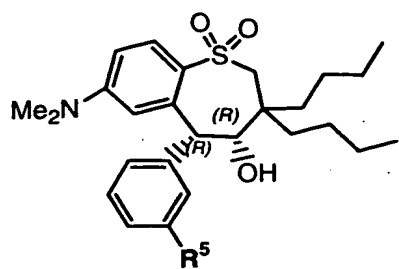


[1344] 1,4-Diazabicyclo(2.2.2)octane (0.157g, 1.40 mmol) and acetonitrile (1.00 mL) were combined in a 10 mL round-bottom flask. The reaction flask was purged with N_2 and equipped with magnetic stirrer. A solution of the product of Example 1436 (0.262g, 0.418 mmol) in acetonitrile (2.70 mL) was added. After 2.5 hrs, a white precipitate had had formed. Ethyl ether (6.0 mL) was added, and the precipitate was filtered, washed with ethyl ether, and dried *in vacuo* to yield a white solid (0.250g, 80%). mp 246.0-248.0 $^\circ\text{C}$; ^1H NMR (CD_3OD) δ 0.88 (m, 6H), 1.03-1.55 (m, 10H), 1.76 (m, 1H), 2.11 (m, 1H), 2.74 (s, 6H), 3.11 (m, 8H), 3.37 (m, 6H), 4.12 (s, 1H), 4.39 (s, 2H), 5.31 (s, 1H), 6.11 (s, 1H), 6.52 (dd, J = 8.7, 1.8 Hz, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 6.9 Hz, 1H), 7.32-7.38 (m, 2H), 7.47 (m, 2H), 7.58 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H). HRMS. Calculated for $\text{C}_{40}\text{H}_{56}\text{N}_5\text{O}_4\text{SCl}$: 702.4053. Found:

702.4064. Anal. Calculated for $C_{40}H_{56}N_5O_4SCl$: C, 65.06; H, 7.64; N, 9.48; S, 4.34; Cl, 4.80. Found: C, 64.90; H, 7.77; N, 9.42; S, 4.16; Cl, 4.89.

[1345] Examples 1438 - 1454

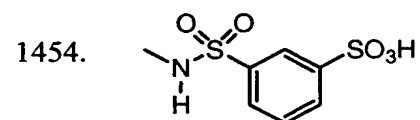
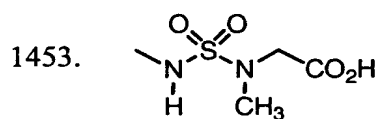
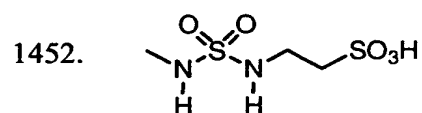
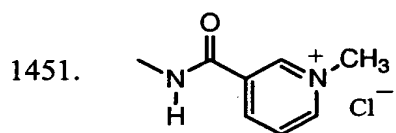
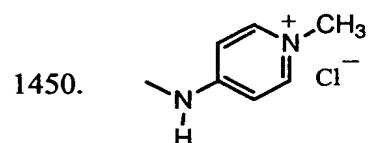
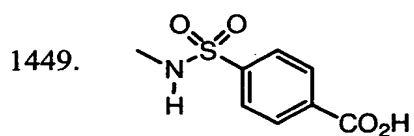
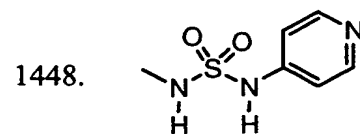
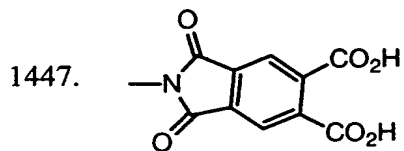
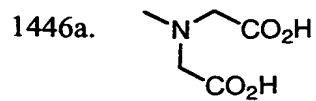
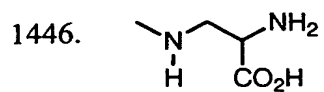
[1346] The compounds of Examples 1438 through 1454 can be prepared in accordance with one or more of the synthetic schemes previously disclosed in this application or using methods known to those skilled in the art.



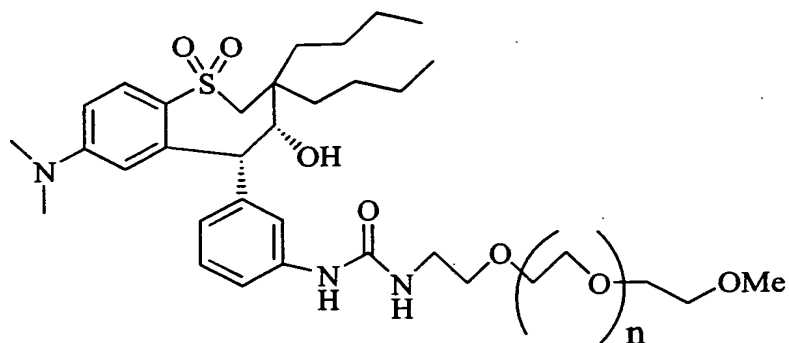
R⁵

- 1438.
- 1439.
- 1440.
- 1441.
- 1442.
- 1443.
- 1444.
- 1445.

R⁵



[1347] Example 1455

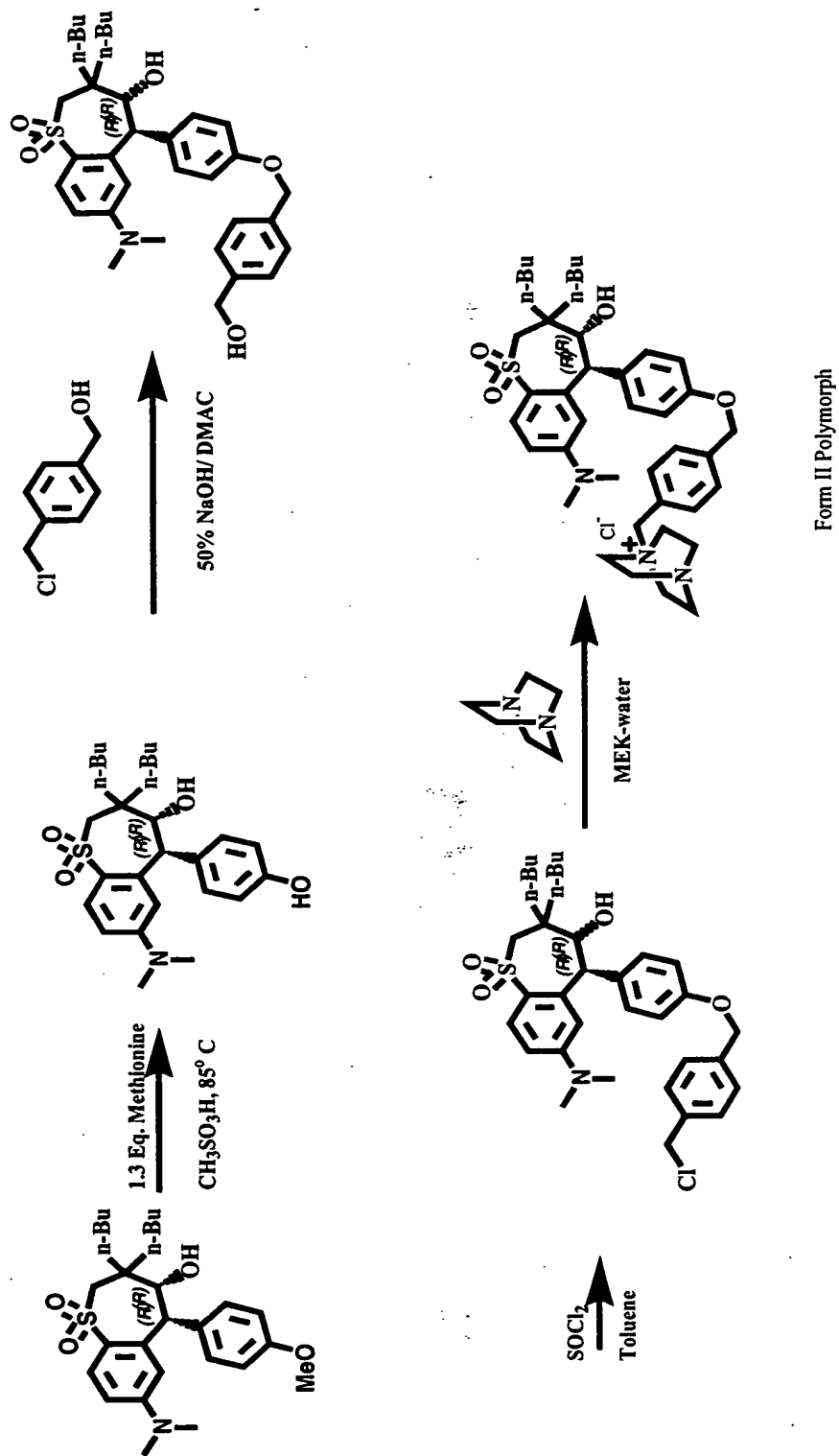


[1348] The 3-aminobenzothiepine of step 5 of Example 1398 (0.0165g/0.0360 mmol), M-NCO-5000 (0.150g/0.30 mmol) (Methoxy-PEG-NCO, MW 5000, purchased from Shearwater Polymers Inc., 2130 Memorial Parkway, SW, Huntsville, Alabama 35801), and CDCl_3 (0.7 mL) were combined in an 8 mm NMR tube. The tube was purged with N_2 . After 72 hrs, the reaction mixture was heated to 50 °C. After 24 hrs, an additional aliquot of the 3-aminobenzothiepine of step 5 of Example 1398 (0.0077g/0.017 mmol) was added. After 24 hrs, the reaction mixture was transferred to a 2 mL vial and evaporated to dryness with a N_2 purge. The resulting white solid was dissolved in hot ethyl ether (2.0 mL) and ethyl acetate (0.057 mL/4 drops), cooled to precipitate and filtered. This precipitation procedure was repeated until no starting material was detected in the precipitate (TLC: SiO_2 /80% EtOAc/hexanes). Concentrated *in vacuo* to give a white solid (0.0838g/51%). ^1H NMR (CDCl_3) δ 0.82-0.90 (m, 6H), 1.05-1.49 (m, 14H), 1.18 (t, J = 6.8 Hz, 2H), 1.59 (bt, 1H), 2.18 (bt, 1H), 2.34 (s, 2H), 2.78 (s, 6H), 3.04 (ABq, 2H), 3.35-3.80 (m, 625H), 4.09 (d, J = 7.2 Hz, 2H), 5.42 (s, 1H), 5.78 (s, 1H), 6.04 (d, J = 1.6 Hz, 1H), 6.47 (dd, J = 6.4, 3.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.31 (bs, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H). Mass spectroscopy data also verified desired product.

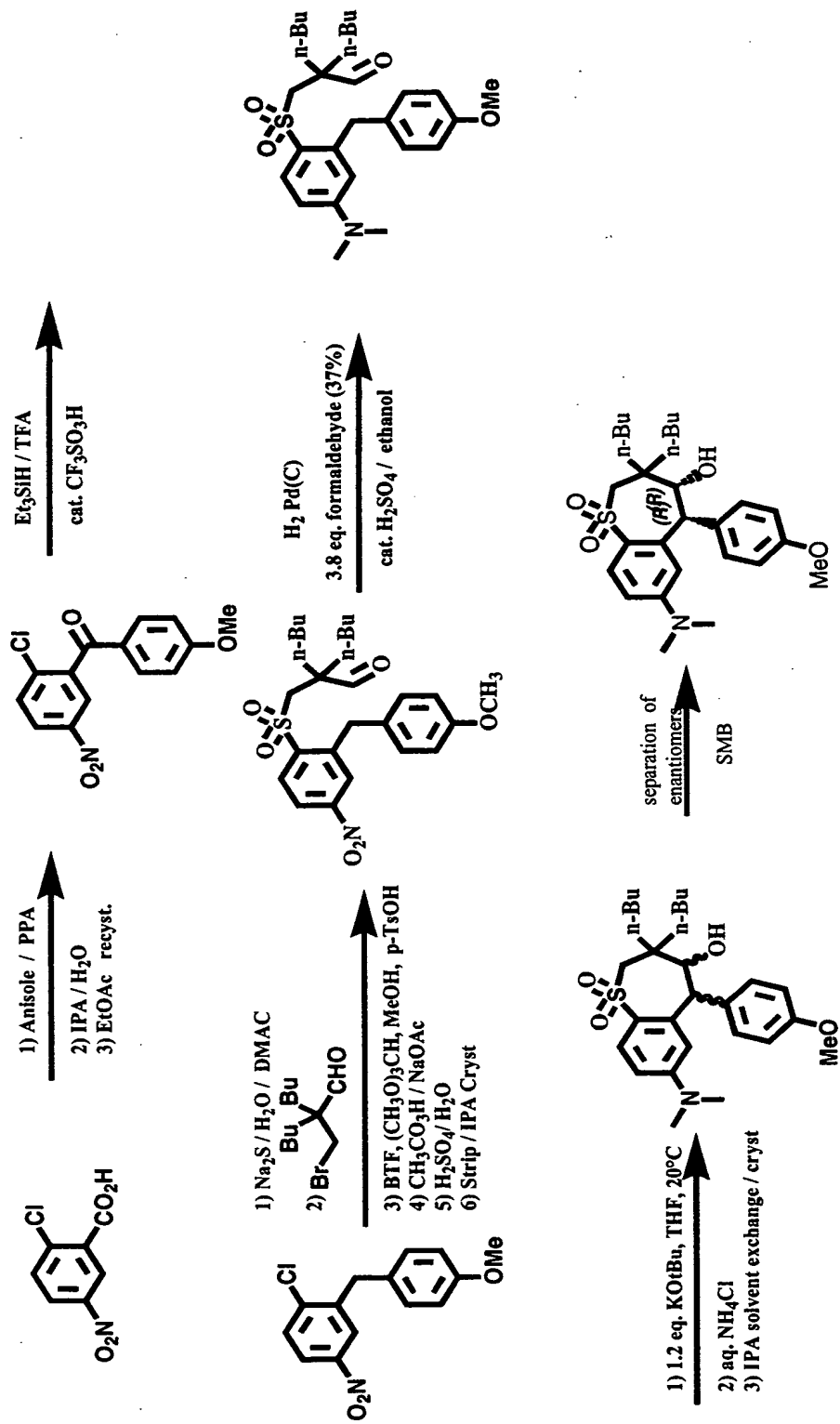
[1349] Additional Examples

[1350] Additional schemes for forming compounds of the present invention are provided below.

Scheme 12



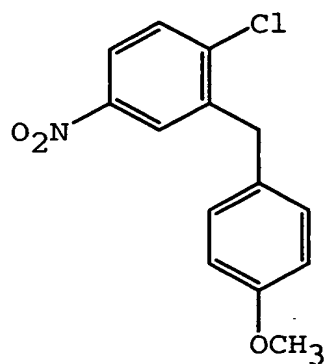
Scheme 13



[1351] Generally, the process methods of the present invention can be performed as follows.

[1352] Example 1456

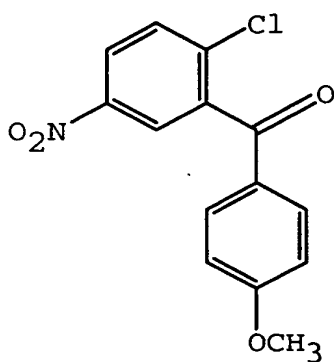
[1353] Preparation of 1-chloro-2-(4-methoxyphenyl)methyl-4-nitrobenzene, 33x



33x

[1354] Step A. Preparation of 2-chloro-5-nitrophenyl-4'-methoxyphenyl ketone, 34x.

[1355] Method 1



34x

[1356] In an inert atmosphere, weigh out 68.3 g of phosphorus pentachloride (0.328 mole, Aldrich) into a 2-necked 500 mL round bottom flask. Fit the

flask with a N₂ inlet adapter and suba seal. Remove from the inert atmosphere and begin N₂ purge. Add 50 mL of anhydrous chlorobenzene (Aldrich) to the PCl₅ via syringe and begin stirring with a magnetic stir bar.

[1357] Weigh out 60 g of 2-chloro-5-nitrobenzoic acid (0.298 mole, Aldrich). Slowly add the 2-chloro-5-nitrobenzoic acid to the chlorobenzene solution while under N₂ purge. Stir at room temperature overnight. After stirring at room temperature for about 20 hrs, place in an oil bath and heat at 50°C for 1 hr. Remove chlorobenzene under high vacuum. Wash the residue with anhydrous hexane. Dry the acid chloride (wt = 61.95 g). Store in inert and dry atmosphere.

[1358] In an inert atmosphere, dissolve the acid chloride in 105 mL of anhydrous anisole (0.97 mole, Aldrich). Place solution in a 2-neck 500 mL round bottom flask.

[1359] Weigh out 45.1 g of aluminum trichloride (0.34 moles, Aldrich) and place in a solid addition funnel. Fit the reaction flask with an addition funnel and a N₂ inlet adapter. Remove from inert atmosphere. Chill the reaction solution with an ice bath and begin the N₂ purge. Slowly add the AlCl₃ to the chilled solution. After addition is complete, allow to warm to room temperature. Stir overnight.

[1360] Quench the reaction by pouring into a solution of 300 mL 1N HCl and ice. Stir for 15 min. Extract twice with ether. Combine the organic layers and extract twice with 2% NaOH, then twice with deionized H₂O. Dry over MgSO₄, filter, and rotovap to dryness. Remove the anisole under high vacuum. Crystallize the product from 90% ethanol/10% ethyl acetate. Dry on a vacuum line. Wt = 35.2 g. yield 41%. Mass spec (m/z = 292).

[1361] Method 2

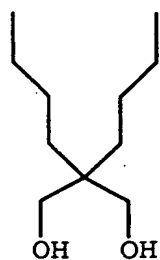
[1362] Change 230 kg of 2-chloro-5-nitrobenzoic acid (CNBA) to a clean dry reactor flushed with N₂. Seal the reactor and flush with N₂. To the reactor charge 460 kg of anisole. Start agitation and heat the mixture to 90°C, dissolving most of the CNBA. To the reactor charge 785 kg of polyphosphoric acid (PPA). PPA containers are warmed in a hot box (70°C) prior to charging in order to lower viscosity. Two phases result. The upper phase contains the majority of the CNBA and anisole. The lower phase contains most of the PPA. The reaction conditions are maintained for 5 hr at which time sampling begins to determine residual CNBA. Analysis of samples is by gas chromatography. The reaction is quenched when 1.0% residual CNBA is achieved. The reaction is quenched into 796 kg H₂O. The temperature of the quenched mass is adjusted to 60°C and maintained at this temperature until isolation. Agitation is stopped and the phases are split. The lower spent acid phase is sent to waste disposal. The upper product phase is washed with 18 kg of sodium bicarbonate in 203 kg of water, then washed with 114 kg of potable water. Agitation is stopped and the phases are split. The upper aqueous phase is sent to waste disposal. The lower product phase is cooled to about 0°C and 312 kg of heptane is added. A mixture of ortho- and para-substituted product (total 10 kg) precipitates out of solution and is recovered by pressure filtration. To the product phase is added another 134 kg of heptane causing another 317 kg of a mixture of ortho- and para-substituted product to precipitate. The precipitate is recovered by pressure filtration. The wetcake is washed with heptane to remove residual anisole. The wetcake is dried in a rotary vacuum dryer at 60°C. Final yield of 34x is 65.1% (30.3% yield of the ortho-substituted product).

[1363] Step B. Preparation of 1-chloro-2-(4-methoxyphenyl)methyl-4-nitrobenzene, 33x.

[1364] To a clean dry nitrogen purged 500 mL round bottom flask was charged 60.0 g (0.206 moles) of 34x. Trifluoroacetic acid (100 grams, ca. 67 mL) was added to the reactor and the resulting suspension was heated to 30°C to give a homogeneous wine colored solution. Next, 71.0 g (0.611 moles) of triethylsilane was placed in an addition funnel and 1.7 g (0.011 moles) of trifluoromethanesulfonic acid (triflic acid) was added to reactor. The color changed from burgundy to greenish brown. Triethylsilane was added dropwise to the solution at 30°C. The batch color changed to a grass green and an exothermic reaction ensued. The exotherm was allowed to raise the batch temperature to 45°C with minimal cooling in a water bath. The reaction temperature was controlled between 45-50°C for the duration of addition. Addition of triethylsilane was complete in 1 hour. The batch color became greenish brown at completion. The batch was stirred for three more hours at 40°C, then allowed to cool. When the batch temperature reached ca. 30°C, product started to crystallize. The batch was further cooled to 1-2°C in a water/ice bath, and after stirring for another half hour at 1-2°C, the slurry was filtered. The crystalline solid was washed with two 60 mL portions of hexane, the first as a displacement wash and the second as a reslurry on the filter. The solids were vacuum filtered until dry on the filter under a stream of nitrogen and the solids were then transferred to a clean container. A total of 49.9 grams of material was isolated. Mp 87.5-90.5°C and HNMR identical with known samples of 33x. GC (HP-5 25 meter column, 1 mL N₂/min at 100°C, FID detection at 300°C, split 50:1) of the product showed homogeneous material. The isolated yield was 88% of 33x.

[1365] Example 1457

[1366] Preparation of 2,2-dibutyl-1,3-propanediol, 54x.



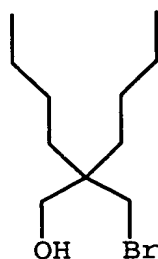
54x

[1367] (This method is similar to that described in U.S. Patent No. 5,994,391, Example Corresponding to Scheme XI, Step 1, column 264.) Lithium aluminum hydride (662 ml, 1.2 equivalents, 0.66 mol) in 662 mL of 1M THF was added dropwise to a stirred solution of dibutyl-diethylmalonate (150 g, 0.55 mol) (Aldrich) in dry THF (700ml) while maintaining the temperature of the reaction mixture at between about -20°C to about 0°C using an acetone/dry ice bath. The reaction mixture was then stirred at room temperature overnight. The reaction was cooled to -20°C and 40 ml of water, 80 ml of 10% NaOH and 80 ml of water were successively added dropwise. The resulting suspension was filtered. The filtrate was dried over sodium sulfate and concentrated under vacuum to give 98.4 g (yield 95%) of the diol as an oil. Proton NMR, carbon NMR and MS confirmed the product.

[1368] Alternate reducing agents that will be useful in this preparation of compound **54x** include diisobutylaluminum hydride (DIBAL-H) or sodium bis(2-methoxyethoxy)aluminum hydride (for example, Red-Al supplied by Aldrich).

[1369] Example 1458

[1370] Preparation of 1-bromo-2-butyl-2-(hydroxymethyl)hexane, **52x**.



52x

[1371] A 250 mL 3-necked round-bottomed flask was fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel or condenser or distilling head with receiver, a thermocouple connected to a J-Kem temperature controller and a thermocouple connected to analog data acquisition software, and a heating mantle. The flask was purged with nitrogen and charged with 20 grams of **54x**. To this was added 57 grams of a 30 wt. % solution of HBr in acetic acid. The mixture was heated to 80°C for 4 hrs. The solvents were distilled off to a pot temperature of 125°C over 20 minutes. This removes most of the residual HBr. The mixture was cooled to 80°C and 100 mL of Ethanol 2B (source: Aaper) was added at once. Next 1.0 mL of concentrated sulfuric acid was added. The solvent was distilled off (10 to 15 ml solvent at 79-80°C). And the mixture was refluxed for 2h. An additional 10 to 15 ml of solvent was distilled off and the mixture was again held at reflux temperature for 2h. Further solvent was distilled off to a pot temperature of 125°C and then the flask contents were cooled to 25.0°C. To the flask was added 100 mL of ethyl acetate and 100 mL of 2.5N sodium hydroxide. The mixture was agitated for 15 minutes and the aqueous layer was separated. Another 100 mL of water was added to the pot and the contents were agitated 15 minutes. The aqueous layer was separated and solvent was distilled off to a pot temperature of 125°C. During this process water is removed by azeotropic distillation with ethyl acetate. The product was concentrated under reduced pressure to afford 26.8 g of a brown oil containing the

product 52x (96.81% by GC: HP1 column; initial temp. 50°C, hold for 2.5 min, Ramp 10°C/min to ending temp. 275°C, final time 15 min).

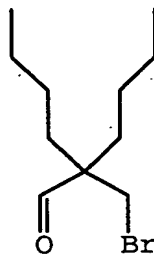
[1372] Example 1458a

[1373] Alternate Preparation of 1-bromo-2-butyl-2-(hydroxymethyl)hexane, 52x.

[1374] A 250 mL 3-necked round-bottomed flask is fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel or condenser or distilling head with receiver, a thermocouple connected to a J-Kem temperature controller and a thermocouple connected to analog data acquisition software, and a heating mantle. The flask is purged with nitrogen and charged with 20 grams of 54x. To this is added 57 grams of a 30 wt. % solution of HBr in acetic acid. The mixture is heated to 80°C for 4 hrs. The solvents are vacuum distilled off to a pot temperature of 90°C over 20 minutes. This removes most of the residual HBr. The mixture is cooled to 80°C and 100 mL of Ethanol 2B (source: Aaper) is added at once. Next 1.0 mL of concentrated sulfuric acid is added. The solvent is distilled off (10 to 15 ml solvent at 79-80°C). And the mixture is refluxed for 2h. An additional 10 to 15 ml of solvent is distilled off and the mixture is again held at reflux temperature for 2h. Further solvent is distilled off to a pot temperature of 85°C and then the flask contents are cooled to 25.0°C. To the flask is added 100 mL of ethyl acetate and 100 mL of 2.5N sodium hydroxide. The mixture is agitated for 15 minutes and the aqueous layer is separated. Another 100 mL of water is added to the pot and the contents are agitated 15 minutes. The aqueous layer is separated and solvent is distilled off to a pot temperature of 85°C. During this process water is removed by azeotropic distillation with ethyl acetate. The material is concentrated under reduced pressure to afford the product 52x.

[1375] Example 1459

[1376] Preparation of 2-(bromomethyl)-2-butylhexanal, 53x.



53x

[1377] A 500 mL 3-necked round-bottom flask was fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel or condenser or distilling head with receiver, a thermocouple connected to a J-Kem temperature controller and a thermocouple connected to analog data acquisition software, and a heating mantle. The flask was purged with nitrogen gas and charged with 26.0 grams of 52x and 15.6 grams of triethylamine. In a 250 mL flask was slurried 37.6 grams of sulfur trioxide-pyridine in 50 mL of DMSO. The DMSO slurry was added to the round-bottom flask by addition funnel over 15 min. The addition temperature started at 22°C and reached a maximum of 41.0°C. (Addition of the slurry at temperatures below 18.0°C will result in a very slow reaction, building up sulfur trioxide which will react rapidly when the temperature rises above 25°C.) The mixture was stirred for 15 minutes. To the mixture was added 100 mL of 2.5M HCl over 5 minutes. The temperature was maintained below 35°C. Next, 100 mL of ethyl acetate was added and the mixture was stirred 15 minutes. The mixture was then cooled to ambient and the aqueous layer was separated. To the pot was added 100 mL of water and the mixture was agitated for 15 minutes. The aqueous layer was separated. The solvent was distilled to a pot temperature of 115°C and the remaining material was concentrated under reduced pressure to

afford 21.8 g of a brown oil containing the product 53x (95.1% by GC: HP1 column; initial temp. 50°C, hold for 2.5 min, Ramp 10°C/min to ending temp. 275°C, final time 15 min).

[1378] Example 1459a

[1379] Alternate Preparation and Purification of 2-(Bromomethyl)-2-butylhexanal, 53x.

[1380] a. Preparation of Compound 52x

[1381] To the reactor is charged 2,2-dibutyl-1,3-propanediol followed by 30 wt% HBr in acetic acid. The vessel is sealed and heated at an internal temperature of ca. 80°C and held for a period of ca. 7 hours, pressure maintained below 25 psia. A GC of the reaction mixture is taken to determine reaction completion (i.e., conversion of 2,2-dibutyl-1,3-propanediol into 3-acetoxy-2,2-dibutyl-1-propanol). If the reaction is not complete at this point, the mixture may be heated for an additional period of time to complete the conversion. Acetic acid/HBr is then removed using house vacuum (ca. 25 mmHg) up to a maximum internal temperature of ca. 90°C. Ethanol is then added followed by sulfuric acid. A portion of the ethanol is removed (ca. one-quarter of the ethanol added) via atmospheric distillation. Ethanol is then added back (ca. the amount removed during the distillation) to the reactor containing the 3-acetoxy-2,2-dibutyl-1-propanol and the contents are heated to reflux (ca. 80°C with a jacket temperature of 95°C) and then held at reflux for ca. 8 hours. Ethanol is then removed via atmospheric distillation up to a maximum internal temperature of 85°C, using a jacket temperature of 95°C. A GC is taken to determine reaction completion (i.e., conversion of 3-acetoxy-2,2-dibutyl-1-propanol to compound 52x). If the reaction is not complete, ethanol is added back to the reactor and the contents are heated to reflux and then held at reflux for an additional 4 hours (ca. 80°C, with a jacket of 95°C). Ethanol is then removed via atmospheric distillation up to a maximum internal temperature of 85°C, using a jacket temperature of

95°C. A GC is taken to determine reaction completion (i.e., conversion of 3-acetoxy-2,2-dibutyl-1-propanol to compound 52x). Once the reaction is deemed to be complete, the remaining ethanol is removed via atmospheric distillation up to a maximum internal temperature of 125°C. Methyl t-butyl ether is then added followed by a 5% sodium bicarbonate solution. The layers are separated, the aqueous layer is extracted once with MTBE, the organic extracts are combined, washed once with water, dried over MgSO₄, and concentrated under house vacuum (ca. 25 mmHg) to a maximum internal temperature of 60°C. The resultant oil is stored in the cooler until it is needed for further processing.

[1382] b. Preparation of Compound 53x.

[1383] Methyl sulfoxide is charged to the reactor followed by compound 52x and triethylamine. Pyridine-sulfur trioxide complex is then added portion-wise to the reactor while maintaining an internal temperature of <35°C. Once the pyridine-sulfur trioxide complex addition is complete, a GC of the reaction mixture is taken to determine reaction completion (i.e., conversion of 52x into 53x). If the reaction is not complete at this point, the mixture may be stirred for an additional period of time to complete the conversion. The reaction is quenched with an 11 wt% aqueous HCl solution. Ethyl acetate is added and the layers are separated, the aqueous layer is extracted once with ethyl acetate, the organic extracts are combined, washed once with water, dried over MgSO₄, and concentrated under house vacuum (ca. 25 mm/Hg) to a maximum internal temperature of 30°C. The resultant oil is stored in the cooler until it is needed for further processing.

[1384] c. Alternate Preparation of Compound 53x.

[1385] Compound 52x and methylene chloride are charged to the reactor followed by TEMPO. The solution is cooled to ca. 0-5°C. Potassium bromide and sodium bicarbonate are dissolved in a separate reactor and added to the solution of 52x and TEMPO at 0-5°C. The biphasic mixture

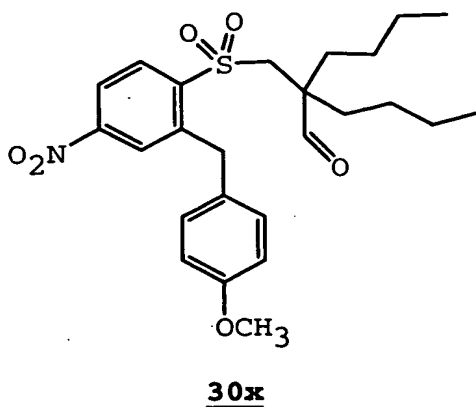
is cooled to 0-5°C and sodium hypochlorite is added at such a rate to maintain an internal temperature of 0-5°C. When the add is complete a GC of the reaction mixture is performed to determine reaction completion. If the reaction is not complete ($>1\%$ 52x remaining), additional sodium hypochlorite may be added to drive the reaction to completion. Immediately after the reaction is determined to be complete, an aqueous solution of sodium sulfite is added to quench the remaining sodium hypochlorite. The layers are separated, the aqueous layer is back-extracted with methylene chloride, the combined organic fractions are washed and dried over sodium sulfate. Compound 53x is then concentrated via a vacuum distillation, up to a maximum internal temperature of ca. 30°C. The crude aldehyde is stored in the cooler until it is required for further processing.

[1386] d. Purification of Compound 53x.

[1387] A Wiped Film Evaporated (WFE) apparatus is set up with the following conditions: evaporator temperature of 90°C, vacuum of ca. 0.2 mmHg and a wiper speed of 800 rpm's. The crude compound 53x is fed at a rate of 1.0-1.5 kilograms of crude per hour. The approximate ratio of product to residue during distillation is 90:10.

[1388] Example 1460

[1389] Preparation of 1-(2,2-dibutyl-S,S-dioxido-3-oxopropylthio)-2-((4-methoxyphenyl)methyl)-4-nitrobenzene, 30x



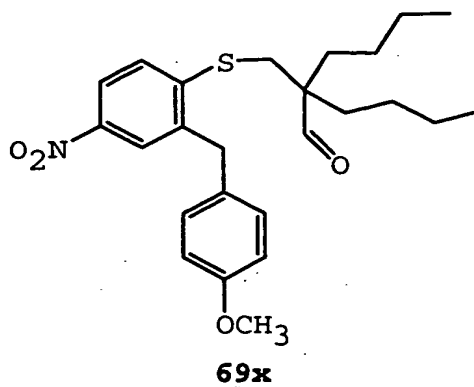
[1390] A 1000 mL 4 neck jacketed Ace flask was fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel or condenser or distilling head with receiver, a thermocouple, four internal baffles and a 28 mm Teflon turbine agitator. The flask was purged with nitrogen and charged with 75.0 grams of **33x**. Next, the flask was charged with 315.0 grams of dimethylacetamide (DMAC), agitation was started and the mixture was heated to 30°C. Sodium sulfide (39.2 grams) was dissolved in 90 ml water in a separate flask. The aqueous sodium sulfide solution was charged into the flask over a 25 minute period. Temperature reached 37°C at completion of addition. The solution turned dark red immediately and appeared to form a small amount of foam-like globules that adhered to the wall of the reactor. The temperature was held for two hrs at 40°C. To the flask was charged 77.9 grams of **53x** all at once. The reaction mixture was heated to 65°C and held for 2 hrs. Next 270 ml water was added at 65°C. The mixture was agitated 15 minutes. To the flask was then charge 315 ml of benzotrifluoride and the mixture was agitated 15 minutes. The aqueous layer was separated at 50°C. The organic layer was washed with 315 ml of 3% sodium chloride solution. The aqueous layer was separated at 50°C. The solvent was distilled to a pot temperature of 63°C at 195 to 200 mmHg. The flask contents were cooled to 60°C and to it was charged 87.7 grams of trimethyl orthoformate, and 5.2 grams of p-toluenesulfonic acid dissolved in 164.1 mL of methanol. The mixture was heated to reflux, 60 to 65°C for 2

hours. The solvent was distilled to a pot temperature of 63°C at 195 to 200 mmHg to remove methanol and methylformate. The flask was then charged with 252 ml benzotrifluoride and then cooled to 15°C. Next 22.2 grams sodium acetate as a slurry in 30 ml water was added to the flask. The flask was then charged with 256.7 grams of commercial peracetic acid (nominally 30 - 35% assay) over 20 minutes, starting at 15°C and allowing the exotherm to reach 30 to 35°C. The addition was slow at first to control initial exotherm. After the first equivalent was charged the exotherm subsided. The mixture was heated to 30°C and held for 3 hours. The aqueous layer was separated at 30°C. The organic layer was washed with 315 ml 6% sodium sulfite. The aqueous layer was separated. The flask was then charged with 40% by wt. sulfuric acid and heated to 75°C for 2 hrs. The aqueous layer was separated from the bottom at 40 to 50°C. To the flask was added 315 ml saturated sodium bicarbonate and the contents were stirred for 15 minutes. The aqueous layer was separated. The solvent was distilled to a reactor temperature of 63°C at 195 to 200 mmHg. Next, 600 ml isopropyl alcohol was charged over 10 minutes and the temperature was maintained at 50°C. The reactor was cooled to 38°C and held for 1 hour. (The product may oil slightly at first then crystallize during the hold period. If product oils out at 38°C or does not crystallize it should be seeded to promote crystallization before cooling.) The reactor was cooled to 15°C over 30 minutes then held for 60 minutes. The solids were filtered and dried to yield 102.1 grams of a crystalline yellow solid. Wash with 150 ml 10°C IPA. Analysis by HPLC (Zorbax RX-C8 column, 0.1% aq. TFA/acetonitrile gradient mobile phase, UV detection at 225 nm) showed 97.7% by weight of 30x, 79.4% isolated molar corrected yield.

[1391] Example 1460a

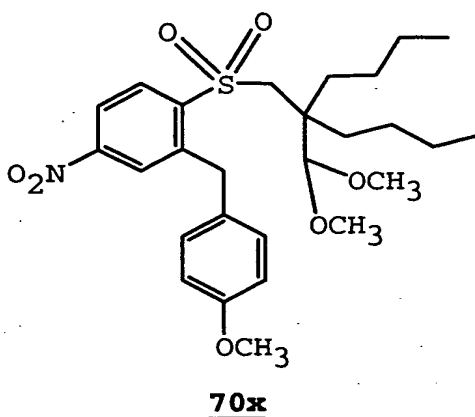
[1392] Alternate Preparation of 1-(2,2-dibutyl-S,S-dioxido-3-oxopropylthio)-2-((4-methoxyphenyl)methyl)-4-nitrobenzene, 30x

[1393] Step 1. Preparation of sulfide aldehyde compound 69x.



[1394] A 1000 mL 4 neck jacketed Ace reator is fitted with a mechanical stirrer, nitrogen inlet, additional funnel, a thermocouple, four internal baffles, and a 28 mm Teflon turbine agitator. The flask is purged with nitrogen gas and charged with 145 g of compound 33x and 609 mL of N,N-dimethylacetamide (DMAC). Agitation is started and the mixture is heated to 30°C. In a separate flask 72.3 g of Na₂S (Spectrum) is dissolved in 166.3 mL of water. The aqueous Na₂S is charged to the flask over a period of about 90 minutes. Addition rate should be adjusted to maintain the reaction temperature below 35°C. The mixture is stirred at 35°C for 2 hours and then 150.7 g of compound 53x is added all at once. The mixture is heated to 70°C and held for 2 hours. To the mixture is adjusted to 50°C, to it is added 442.7 mL water and the mixture is agitated for 15 minutes. To the reactor is then charged 609 mL of benzotrifluoride followed by 15 minutes of agitation. The aqueous layer is separated at 50°C. The organic layer is washed with 3% aq. NaCl. The aqueous layer is separated at 50°C. The organic layer contains compound 69x. The organic layer is stable and can be held indefinitely.

[1395] Step 2. Preparation of Compound **70x**.



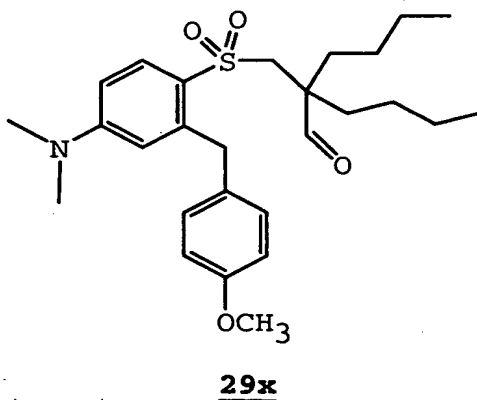
[1396] The solvent is distilled at about 63°C to 66°C and 195 to 200 mmHg from the organic layer resulting from Step 1 until a third to a half of the benzotrifluoride volume is distilled. The mixture is cooled to about 60°C and charged with 169.6 g of trimethylorthoformate and about 10 g of p-toluenesulfonic acid dissolved in 317.2 mL of methanol. (Note: alternate orthoformates, for example triethylorthoformate, can be used in place of trimethylorthoformate to obtain other acetals.) The reactor is fitted with a condenser and a distillation head. The mixture is heated to boiling and from it is distilled 5 mL of methanol to remove residual water from the condenser and the mixture is held at reflux at 60°C to 65°C for about 2 hours. Solvent is then distilled to a pot temperature of 60°C to 66°C at 195 to 200 mm Hg to remove methanol and methylformate. To the mixture is added 355.4 mL benzotrifluoride and the mixture is cooled to 15°C. To the reactor is charged 32.1 g sodium acetate slurried in 77.2 mL water. The reaction is held for 72 hours. To the reactor is then charged 340.4 g of peracetic acid over a 2 hour period starting at 15°C. Addition was adjusted to keep the temperature at or below 20°C. The mixture was then heated to 25°C for 4 hours. The aqueous (top) layer was separated at 25°C and the organic layer was washed with 190 mL of 10% sodium sulfite. The organic layer contains compound **70x** and can be stored indefinitely.

[1397] Step 3. Preparation of Compound 30x.

[1398] To the organic layer of Step 2 is added 383.8 g of concentrated sulfuric acid. The mixture is heated at 75°C for 2 hours and the aqueous (bottom) layer is separated at 40 to 50°C. To the reactor is charged 609 mL of 10% sodium bicarbonate and the mixture is stirred for 15 minutes. The aqueous (top) layer is separated. Solvent is distilled from the organic layer at 63 to 66°C at 195 to 200 mm Hg. To the reactor is charged 1160 mL of isopropyl alcohol over 10 minutes at 50°C. The reactor is cooled to 38°C and held for 1 hour. Some crystallization occurs. The reactor is cooled to 15°C over 30 minutes and held for 120 minutes, causing further crystallization of 30x. The crystals are filtered and dried to yield 200.0 g of a crystalline yellow solid. The crystals of 30x are washed with 290 mL of 10°C isopropyl alcohol.

[1399] Example 1461

[1400] Preparation of 1-(2,2-dibutyl-S,S-dioxido-3-oxopropylthio)-2-((4-methoxyphenyl)methyl)-4-dimethylaminobenzene, 29x.

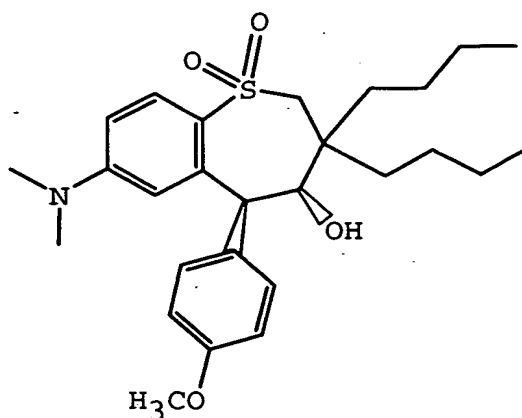


[1401] A 300 ml autoclave was fitted with a Stirrermix hollow shaft gas mixing agitator, an automatic cooling and heating temperature control, and an in-reactor sampling line with sintered metal filter. At 20°C the autoclave was charged with 15.0 grams of 30x, 2.5 grams of Pd/C catalyst, 60 grams of ethanol, 10.0 grams of formaldehyde (36% aqueous solution), and 0.55

grams of concentrated sulfuric acid. The reactor was closed and pressurized the reactor to 60 psig (515 kPa) with nitrogen to check for leakage. The pressure was then reduced to 1-2 psig (108 - 115 kPa). The purge was repeated three times. The autoclave was then pressurized with H₂ to 60 psig (515 kPa) while the reactor temperature was held at 22°C. The agitator was started and set to 800-1000 rpm and the reactor temperature control is set at 30-40°C. When the cooling capacity was not enough to control the temperature, the agitator rpm or the reactor pressure was reduced to maintain the set temperature. After about 45 minutes when the heat release was slowing down (about 70% of hydrogen usage was reacted), the temperature was raised to 60°C. Hydrogen was then released and the autoclave was purged with nitrogen three times. The content of the reactor was pressure filtered through a sintered metal filter at 60°C. The filtrate was stirred to cool to the room temperature over 1-2 hours and 50 grams of water was added over 1 hour. The mixture was stirred slowly at 4°C overnight and filtered through a Buche type filter. The cake was air dried to give 13.0 grams of 29x with 99+% assay. The isolated yield was 89%.

[1402] Example 1462

[1403] Preparation of *syn*-3,3-dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine, *syn*-24x



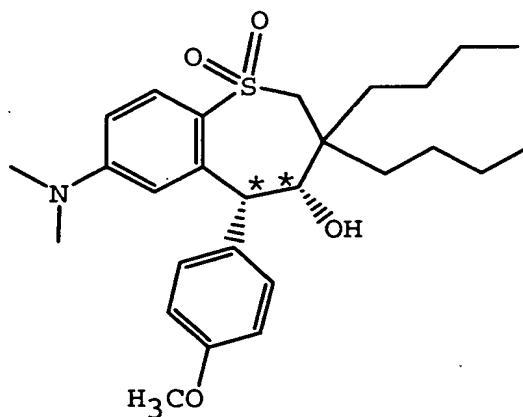
syn-24x

[1404] A 250 ml round bottom glass reactor fitted with mechanical agitator and a heating/cooling bath was purged with nitrogen. Forty-five grams of potassium t-butoxide/THF solution were charged to the reactor and agitation was started. In a separate container 18 grams of 29x was dissolved in 25 grams of THF. The 29x/THF solution was charged into the reactor through a addition funnel over about 2.0 hours. The reactor temperature was controlled between about 16-20°C. Salt precipitated after about half of 29x was added. The slurry was stirred at 16-20°C for an hour. The reaction was quenched with 54 grams of 7.4% ammonium chloride aqueous solution over a period of about 30 minutes while keeping the reactor temperature at 16-24°C. The mixture was gently stirred until all salt is dissolved (about 10 minutes). Agitation was stopped and the phases were allowed to separate. The aqueous layer was drained. The organic layer was charged with 50 ml water and 25 grams of isopropyl alcohol. The agitator was started and crystallization was allowed to take place. The THF was distilled under the ambient pressure, with b.p. from 60 to 65°C and pot temperature from 70 to 77°C. The crystals dissolved as the pot gets heated and reappeared when the THF started to distill. After distillation was complete, the slurry was slowly cooled to 4°C over 2-3 hours and stirred slowly for several hours. The slurry was filtered with a 150 ml Buche filter and the cake was washed with 10 grams of cold 2:1 water/isopropyl alcohol solution. Filtration was

complete in about 5 minutes. The cake was air dried to give 16.7 grams of *syn*-**24x** with 99+% assay and a 50/50 mixture of R,R and S,S isomers.

[1405] Example 1463a

[1406] Conditions for Optical Resolution of Compound (4R,5R)-**24x**



(4R, 5R) - **24x**

[1407] The following simulated moving bed chromatography (SMB) conditions are used to separate the (4R,5R) and (4S,5S) enantiomers of compound *syn*-**24x**.

Column (CSP):	Daicel Chiralpak AS
Mobile Phase:	acetonitrile (100%)
Column Length:	11 cm (9 cm for column 6)
Column I.D.:	20.2 cm
Number of Columns:	6 columns
Feed Concentration:	39 grams/liter
Eluent Flowrate:	182 L/hour
Feed Flowrate:	55 L/hour
Extract Flowrate:	129.4 L/hour
Raffinate Flowrate:	107.8 L/hour
Recycling Flowrate:	480.3 L/hour
Period:	0.6 minute
Temperature:	Ambient

[1408] SMB performance:

[1409] Less retained enantiomer purity (%): 92.8 %

[1410] Less retained enantiomer concentration: 10 g/L

[1411] More retained enantiomer recovery yield (%): 99.3 %

[1412] More retained enantiomer concentration: 7 g/L

[1413] Example 1463b

[1414] Alternate Conditions for Optical Resolution of Compound (4R,5R)-24x

[1415] The following simulated moving bed chromatography (SMB) conditions are used to separate the (4R,5R) and (4S,5S) enantiomers of compound *syn*-24x.

Column (CSP):	di-methyl phenyl derivative of tartaric acid (Kromasil DMB)
Mobile Phase:	toluene/methyl tert-butyl ether (70/30)
Column Length:	6.5 cm
Column I.D.:	2.12 cm
Number of Columns:	8 columns
Zones:	2-3-2-1
Feed Concentration:	6.4 weight percent
Eluent Flowrate:	20.3 g/minute
Feed Flowrate:	0.7 g/minute
Extract Flowrate:	5.0 g/minute
Raffinate Flowrate:	16.0 g/minute
Period:	8 minute
Temperature:	Ambient

[1416] SMB performance:

[1417] Less retained enantiomer purity (%): >98%

[1418] Less retained enantiomer recovery yield (%): >95%

[1419] Example 1463c

[1420] Alternate Conditions for Optical Resolution of Compound (4R,5R)-24x

[1421] The following simulated moving bed chromatography (SMB) conditions are used to separate the (4R,5R) and (4S,5S) enantiomers of compound syn-24x.

Column (CSP):	di-methyl phenyl derivative of tartaric acid (Kromasil DMB)
Mobile Phase:	toluene (100%)
Column Length:	6.5 cm
Column I.D.:	2.12 cm
Number of Columns:	8 columns
Zones:	2-3-2-1
Feed Concentration:	64 weight percent
Eluent Flowrate:	20.3 g/minute
Feed Flowrate:	0.5 g/minute
Extract Flowrate:	4.9 g/minute
Raffinate Flowrate:	15.9 g/minute
Period:	8 minute
Temperature:	Ambient

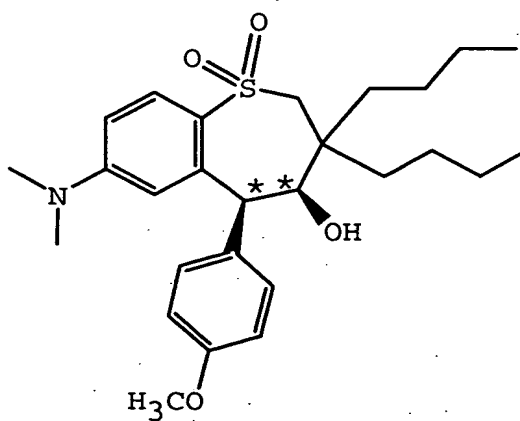
[1422] SMB performance:

[1423] Less retained enantiomer purity (%): >98%

[1424] Less retained enantiomer recovery yield (%): >95%

[1425] Example 1463d

[1426] Racemization of Compound (4S,5S)-24x

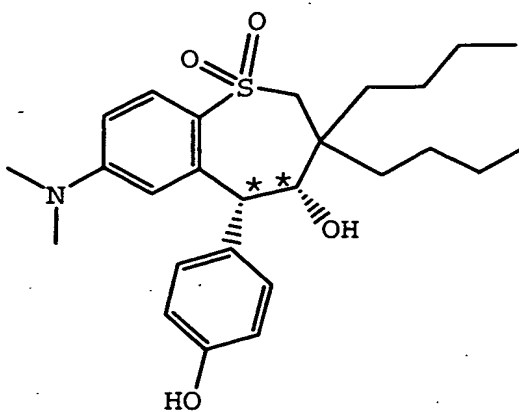


(4S,5S)-24x

[1427] A 250 mL round bottom glass reactor with mechanical agitator and a heating/cooling bath is purged with nitrogen gas. In a flask, 18 g of (4S,5S)-24x (obtained as the more retained enantiomer in Examples 8a - 8c) is dissolved in 50 g of dry THF. This solution is charged into the reactor and brought to about 23-25°C with agitation. To the reactor is charged 45 g of potassium t-butoxide/THF solution (1 M, Aldrich) through an addition funnel over about 0.5 hour. A slurry forms. Stir the slurry at about 24-26°C for about 1-1.5 hours. The reaction is quenched with 54 g of 7.5% aqueous ammonium chloride while keeping the reactor temperature at about 23-26°C. The first ca. 20% of the ammonium chloride solution is charged slowly until the slurry turns thin and the rest of the ammonium chloride solution is charged over about 0.5 hour. The mixture is stirred gently until all the salt is dissolved. The agitation is stopped and the phases are allowed to separate. The aqueous layer is removed. To the organic layer is charged 50 mL of water and 25 g of isopropyl alcohol. The agitator is started and crystallization is allowed to take place. THF is removed by distillation at ambient pressure. The crystals dissolve as the pot warms and then reappear when the THF starts to distill. The resulting slurry is cooled slowly to 4°C within 2-3 hours and slowly stirred for 1-2 hours. The slurry is filtered with a 150 mL Buche filter and washed with 20 g of 0-4°C isopropyl alcohol. The cake is air dried at about 50-60°C under vacuum to give 16.7 g of racemic 24x.

[1428] Example 1464

[1429] Preparation of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine, (4R,5R)-28x



(4R, 5R) - 28x

[1430] A 1000 mL 4 neck Reliance jacketed reactor flask was fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel, condenser or distillation head with receiver, a thermocouple, and a Teflon paddle agitator. The flask was purged with nitrogen gas and was charged with 41.3 grams of (4R,5R)-24x and 18.7 grams of methionine followed by 240 grams of methanesulfonic acid. The mixture was heated to 75°C and stirred for 8 hrs. The mixture was then cooled to 25°C and charged with 480 mL of 3-pentanone. The solution was homogeneous. Next, the flask was charged with 320 mL of dilution water and was stirred for 15 minutes. The aqueous layer was separated and to the organic layer was added 250 mL of saturated sodium bicarbonate. The mixture was stirred for 15 minutes and the aqueous layer was separated. Solvent was distilled to approximately one-half volume under vacuum at 50°C. The flask was charged with 480 mL of toluene, forming a clear solution. Approximately half the volume of solvent was removed at 100 mmHg. The mixture was cooled to 10°C and stirred overnight. Crystals were filtered and washed with 150 mL cold toluene and allowed to dry under vacuum. Yielded 29.9g with a 96.4 wt% assay. The filtrate was concentrated and toluene was added to give a second crop of 2.5 grams of crystals. A total of 32.1 g of dry off white crystalline (4R,5R)-28x was obtained.

[1431] Example 1464a

[1432] Alternate Preparation of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine, (4R,5R)-28x

[1433] A 1000 mL 4 neck Ace jacketed reactor flask is fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel, condenser or distillation head with receiver, a thermocouple, and a Teflon paddle agitator. The flask is purged with nitrogen gas and is charged with 40.0 grams of (4R,5R)-24x and 17.8 grams of methionine followed by 178.6 grams of methanesulfonic acid. The mixture is heated to 80°C and stirred for 12 hrs. The mixture is then cooled to 15°C and charged with 241.1 mL of water over 30 minutes. The reactor is then charged with 361.7 mL of 3-pentanone. Next, the flask is stirred for 15 minutes. The aqueous layer is separated and to the organic layer is added 361.7 mL of saturated sodium bicarbonate. The mixture is stirred for 15 minutes and the aqueous layer was separated. Solvent is distilled to approximately one-half volume under vacuum at 50°C. Crystals start to form at this time. The flask is charged with 361.7 mL of toluene and the mixture is cooled to 0°C. Crystals are allowed to form. Crystals are filtered and washed with 150 mL cold toluene and allowed to dry under vacuum at 50°C. Yield 34.1g of off-white crystalline (4R,5R)-28x.

[1434] Example 1464b

[1435] Alternate preparation of (4R,5R)-3,3-dibutyl-7-(dimethylamino)-1,1-dioxido-4-hydroxy-5-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine, (4R,5R)-28x

[1436] A first 45 L reactor is purged with nitrogen gas. To it is charged 2.5 kg of (4R,5R)-24x followed by 1.1 kg of methionine and 11.1 kg of methanesulfonic acid. The reaction mixture is heated to 85°C with agitation for 7 hours. The reaction mixture is then cooled to 5°C and 17.5 L of water is slowly charged to the first reactor. The reaction temperature

will reach about 57°C. Next, 17.5 L of methyl isobutyl ketone (MIBK) are charged to the first reactor and the reaction mixture is stirred for 30 minutes. The mixture is allowed to stand for 30 minutes and the layers are separated. The aqueous phase is transferred to a second 45 L reactor and 10 L of MIBK is charged to the second reactor. The second reactor and its contents are stirred for 30 minutes and then allowed to stand for 30 minutes while the layers separate. The organic phase is separated from the second reactor and the two organic phases are combined in the first reactor. To the first reactor is carefully charged 1.4 kg of aqueous sodium bicarbonate. The mixture is stirred for 30 minutes and then allowed to stand for 30 minutes. The phases are separated. If the pH of the aqueous phase is less than 6 then a second bicarbonate wash is performed. After the bicarbonate wash, 15 L of water is charged to the first reactor and the mixture is heated to 40°C. The mixture is stirred for 30 minutes and then allowed to stand for 30 minutes. The phases are separated. The organic phase is concentrated by vacuum distillation so that approximately 5 L of MIBK remain in the concentrate. The distillation starts when the batch temperature is at 35°C at 1 psia. The distillation is complete when the batch temperature reaches about 47.8°C. The batch temperature is then adjusted to 45°C and 20 L of heptane is charged to the product mixture over 20 minutes. The resulting slurry is cooled to 20°C. The product slurry is filtered (10 micron cloth filter) and washed with 8 L of 20% MIBK/heptane solution. The product is dried on the filter at 80°C for 21 hours under vacuum. A total of 2.16 kg of white crystalline (4R,5R)-28x is isolated.

[1437] Example 1464c

[1438] Batch Isolation of Compound (4R,5R)-28x (or Compound (4S,5S)-28x) from Acetonitrile Solution.

[1439] A 1 L reactor is equipped with baffles and a 4-blade radial flow turbine. The reactor is purged with 1L of nitrogen gas and charged with 300 mL of water. The water is stirred at a minimum rate of 300 rpm at 5°C. The reactor is charged with 125-185 mL of (4R,5R)-28x in acetonitrile solution (20% w/w) at a rate of 1.4 mL/min. Upon addition, crystals start to form. After addition of the acetonitrile solution, crystals are filtered through a Buchner funnel. The cake is washed with 3 volumes of water and/or followed by 1-2 volumes of ice cold isopropyl alcohol before drying. Alternatively, this procedure can be used on an acetonitrile solution of (4S,5S)-28x to isolate (4S,5S)-28x.

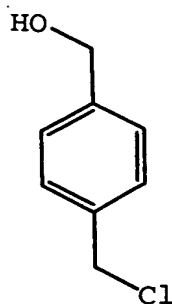
[1440] Example 1464d

[1441] Continuous Isolation of Compound (4R,5R)-28x (or Compound (4S,5S)-28x) from Acetonitrile Solution.

[1442] A 1 L reactor is equipped with baffles and a 4-blade radial flow turbine. The reactor is purged with 1L of nitrogen gas and charged with 60 grams of water and 30 grams of acetonitrile. The mixture is stirred at 300 rpm and 5°C. Into the reactor are fed 300 mL of water and 125 mL of 20% (w/w) (4R,5R)-28x in acetonitrile solution at rates of 1.7 mL/min and 1 mL/min, respectively. When the contents of the reactor reach 70-80% of the volume of the reactor, the slurry can be drained to a filter down to a minimum stirring level in the reactor and followed by more feeding. Alternatively, the reactor can be drained continuously as the feeds continue. The water/acetonitrile ratio can be in the range of about 2:1 to about 3:1. Filtered cake can be handled as described in Example 9c. Alternatively, this procedure can be used on an acetonitrile solution of (4S,5S)-28x to isolate (4S,5S)-28x.

[1443] Example 1465

[1444] Preparation of 1-(chloromethyl)-4-(hydroxymethyl)benzene, 55x

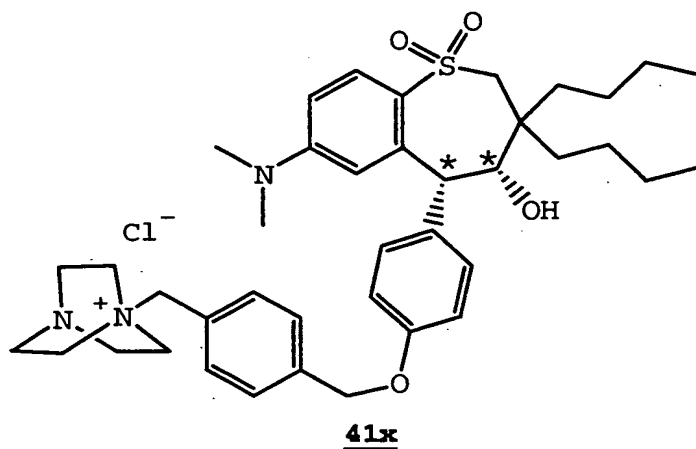


55x

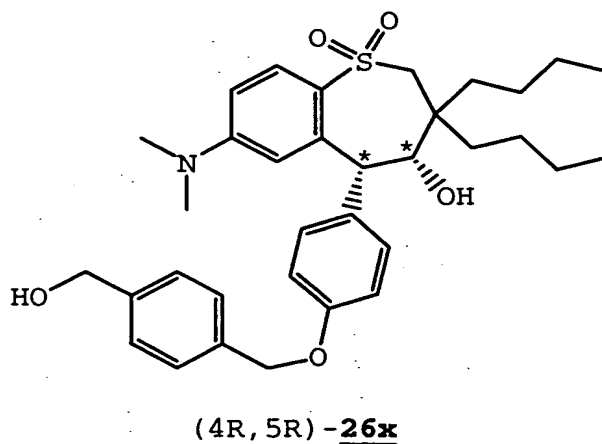
[1445] A reaction flask fitted with a nitrogen inlet and outlet, a reflux condenser, and a magnetic stirrer was purged with nitrogen. The flask was charged with 25g of 4-(chloromethyl)benzoic acid. The flask was charged with 75 mL of THF at ambient temperature. Stirring caused a suspension to form. An endothermic reaction ensued in which the temperature of the reaction mixture dropped 22°C to 14°C. To the reaction mixture 175mL of borane-THF adduct was added via a dropping funnel over about 30 minutes. During this exothermic addition, an ice-bath was used for external cooling to keep the temperature below 30°C. The reaction mixture was stirred at 20°C for 1 h and it was then cooled to 0°C. The reaction mixture was quenched by slow addition of 1M sulfuric acid. The resulting reaction mixture was diluted with 150 mL of t-butyl methyl ether (TBME) and stirred for at least 20 min to destroy boric acid esters. The layers were separated and the aqueous layer was washed with another portion of 50mL of TBME. The combined organic layers were washed twice with 100 mL of saturated sodium bicarbonate solution. The organic layer was dried over 11g of anhydrous sodium sulfate and filtered. The solvents were evaporated on a rotary evaporator at 45°C (bath temperature) and <350 mbar yielding a colorless oil. The oil was seeded with crystals and the resulting solid **55x** was dried under vacuum. Yield: 19.7g (86%). Assay by GC (HP-5 25 meter column, 1 mL N₂/min at 100°C, FID detection at 300°C, split 50:1).

[1446] Example 1466

[1447] Preparation of (4R,5R)-1-((4-(4-(3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzithiepin-5-yl)phenoxy)methyl)phenyl)methyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride, 41x



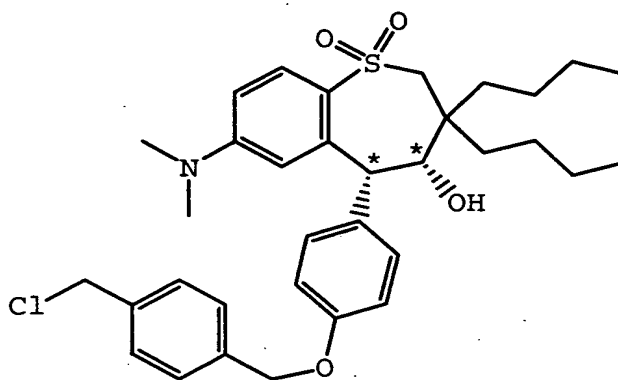
[1448] Step 1. Preparation of (4R,5R)-26x.



[1449] A 1000 mL 4 neck jacketed Ace reactor flask was fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel or condenser or distilling head with receiver, a thermocouple, four internal baffles and a 28 mm Teflon turbine agitator. The flask was purged with nitrogen gas

and charged with 25.0 grams of (4R,5R)-28x and 125 mL of N,N-dimethylacetamide (DMAC). To this was added 4.2 grams of 50% sodium hydroxide. The mixture was heated to 50°C and stirred for 15 minutes. To the flask was added 8.3 grams of 55x dissolved in 10 mL of DMAC, all at once. The temperature was held at 50°C for 24 hrs. To the flask was added 250 mL of toluene followed by 125 mL of dilution water. The mixture was stirred for 15 minutes and the layers were then allowed to separate at 50°C. The flask was then charged with 125 mL of saturated sodium chloride solution and stirred 15 minutes. Layers separated cleanly in 30 seconds at 50°C. Approximately half of the solvent was distilled off under vacuum at 50°C. The residual reaction mixture contained (4R,5R)-26x.

[1450] Step 2. Preparation of (4R,5R)-27x.



(4R, 5R) - 27x

[1451] Toluene was charged back to the reaction mixture of Step 1 and the mixture was cooled to 35°C. To the mixture was then added 7.0 grams of thionyl chloride over 5 minutes. The reaction was exothermic and reached 39°C. The reaction turned cloudy on first addition of thionyl chloride, partially cleared then finally remained cloudy. The mixture was stirred for 0.5 hr and was then washed with 0.25N NaOH. The mixture appeared to form a small amount of solids that diminished on stirring, and the layers cleanly separated. The solvent was distilled to a minimum stir

volume under vacuum at 50°C. The residual reaction mixture contained (4R,5R)-27x.

[1452] Step 3. Preparation of 41x

[1453] To the reaction mixture of Step 2 was charged with 350 mL of methyl ethyl ketone (MEK) followed by 10.5 mL water and 6.4 grams of diazabicyclo[2.2.2]octane (DABCO) dissolved in 10 mL of MEK. The mixture was heated to reflux, and HPLC showed <0.5% of (4R,5R)-27x. The reaction remained homogenous initially then crystallized at the completion of the reaction. An additional 5.3 mL of water was charged to the flask to redissolve product. Approximately 160 mL of solvent was then distilled off at atmospheric pressure. The mixture started to form crystals after 70 mL of solvent was distilled. Water separated out of distillate indicating a ternary azeotrope between toluene, water and methyl ethyl ketone (MEK). The mixture was then cooled to 25°C. The solids were filtered and washed with 150 mL MEK, and let dry under vacuum at 60°C. Isolated 29.8.0 g of off-white crystalline 41x.

[1454] Example 1466a

[1455] Alternate Preparation of (4R,5R)-1-((4-(4-(3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzithiepin-5-yl)phenoxy)methyl)phenyl)methyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride, Form II of 41x

[1456] A 1000 mL 4 neck jacketed Ace reactor flask is fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel or condenser or distilling head with receiver, a thermocouple, four internal baffles and a 28 mm Teflon turbine agitator. The flask is purged with nitrogen gas and charged with 25.0 grams of (4R,5R)-28x and 100 mL of N,N-dimethylacetamide (DMAC). The mixture is heated to 50°C and to it is added 4.02 grams of 50% sodium hydroxide. The mixture is stirred for 30 minutes. To the flask is added 8.7 grams of 55x dissolved in 12.5 mL of DMAC, all at once. The charge vessel is washed with 12.5 mL DMAC and the wash is

added to the reactor. The reactor is stirred for 3 hours. To the reactor is added 0.19 mL of 49.4% aq. NaOH and the mixture is stirred for 2 hours. To the mixture is added 0.9 g DABCO dissolved in 12.5 mL DMAC. The mixture is stirred 30 to 60 minutes at 50°C. To the flask is added 225 mL of toluene followed by 125 mL of dilution water. The mixture is stirred for 15 minutes and the layers are then allowed to separate at 50°C. The bottom aqueous layer is removed but any rag layer is retained. The flask is then charged with 175 mL of 5% hydrochloric acid solution and stirred 15 minutes. Layers are separated at 50°C to remove the bottom aqueous layer, discarding any rag layer with the aqueous layer. Approximately half of the solvent is distilled off under vacuum at a maximum pot temperature of 80°C. The residual reaction mixture contains (4R,5R)-26x.

[1457] Step 2. Preparation of (4R,5R)-27x.

[1458] Toluene (225 mL) is charged back to the reaction mixture of Step 1 and the mixture is cooled to 30°C. To the mixture is then added 6.7 grams of thionyl chloride over 30 to 45 minutes. The temperature is maintained below 35°C. The reaction turns cloudy on first addition of thionyl chloride, then at about 30 minutes the layers go back together and form a clear mixture. The mixture is stirred for 0.5 hr and is then charged with 156.6 mL of 4% NaOH wash over a 30 minute period. The addition of the wash is stopped when the pH of the mixture reaches 8.0 to 10.0. The bottom aqueous layer is removed at 30°C and any rag layer is retained with the organic layer. To the mixture is charged 175 mL of saturated NaCl wash with agitation. The layers are separated at 30°C and the bottom aqueous layer is removed, discarding any rag layer with the aqueous layer. The solvent is distilled to a minimum stir volume under vacuum at 80°C. The residual reaction mixture contains (4R,5R)-27x.

[1459] Step 3. Preparation of 41x.

[1460] To the reaction mixture of Step 2 is charged 325 mL of methyl ethyl ketone (MEK) and 13 mL water. Next, the reactor is charged 6.2 grams

of diazabicyclo[2.2.2]octane (DABCO) dissolved in 25 mL of MEK. The mixture is heated to reflux and held for 30 minutes. Approximately 10% of solvent volume is then distilled off. The mixture starts to form crystals during distillation. The mixture is then cooled to 20°C for 1 hour. The off-white crystalline **41x** (Form II) is filtered and washed with 50 mL MEK, and let dry under vacuum at 100°C.

[1461] Example 1466b

[1462] Alternate Preparation of (4R,5R)-1-((4-(4-(3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzithiepin-5-yl)phenoxy)methyl)phenyl)methyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride, Form II of **41x**

[1463] A 1000 mL 4 neck jacketed Ace reactor flask is fitted with a mechanical stirrer, a nitrogen inlet, an addition funnel or condenser or distilling head with receiver, a thermocouple, four internal baffles and a Teflon turbine agitator. The flask is purged with nitrogen gas and charged with 25.0 grams of (4R,5R)-**28x** and 125 mL of N,N-dimethylacetamide (DMAC). The mixture is heated to 50°C and to it is added 7.11 grams of 30% sodium hydroxide over a period of 15 to 30 minutes with agitation. The mixture is stirred for 30 minutes. To the flask is added 9.5 grams of solid **55x**. The reactor is stirred for 3 hours. To the mixture is added 1.2 g of solid DABCO. The mixture is stirred 30 to 60 minutes at 50°C. To the flask is added 225 mL of toluene followed by 125 mL of water. The mixture is stirred for 15 minutes and the layers are then allowed to separate at 50°C. The bottom aqueous layer is removed but any rag layer is retained with the organic layer. The flask is then charged with 175 mL of 5% hydrochloric acid solution and stirred 15 minutes. Layers are separated at 50°C to remove the bottom aqueous layer, discarding any rag layer with the aqueous layer. The flask is then charged with 225 mL of water and stirred 15 minutes. The layers are allowed to separate at 50°C. The bottom aqueous layer is removed, discarding any rag layer with the aqueous layer. Approximately half of the solvent is distilled off under

vacuum at a maximum pot temperature of 80°C. The residual reaction mixture contains (4R,5R)-26x.

[1464] Step 2. Preparation of (4R,5R)-27x.

[1465] Toluene (112.5 mL) is charged back to the reaction mixture of Step 1 and the mixture is cooled to 25°C. To the mixture is then added 7.3 grams of thionyl chloride over 15 to 45 minutes. The temperature of the mixture is maintained above 20°C and below 40°C. The reaction turns cloudy on first addition of thionyl chloride, then at about 30 minutes the layers go back together and form a clear mixture. The mixture is then charged with 179.5 mL of 4% NaOH wash over a 30 minute period. The mixture is maintained above 20°C and below 40°C during this time. The addition of the wash is stopped when the pH of the mixture reaches 8.0 to 10.0. The mixture is then allowed to separate at 40°C for at least one hour. The bottom aqueous layer is removed and any rag layer is retained with the organic layer. To the mixture is charged 200 mL of dilution water. The mixture is stirred for 15 minutes and then allowed to separate at 40°C for at least one hour. The bottom aqueous layer is removed, discarding any rag layer with the aqueous layer. The solvent is distilled to a minimum stir volume under vacuum at 80°C. The residual reaction mixture contains (4R,5R)-27x.

[1466] Step 3. Preparation of 41x.

[1467] To the reaction mixture of Step 2 is charged 350 mL of methyl ethyl ketone (MEK) and 7 mL water. The mixture is stirred for 15 minutes and the temperature of the mixture is adjusted to 25°C. Next, the reactor is charged with 6.7 grams of solid diazabicyclo[2.2.2]octane (DABCO). The mixture is maintained at 25°C for three to four hours. It is then heated to 65°C and maintained at that temperature for 30 minutes. The mixture is then cooled to 25°C for 1 hour. The off-white crystalline 41x (Form II) is filtered and washed with 50 mL MEK, and let dry under vacuum at 100°C.

[1468] Example 1467

[1469] Alternate preparation of (4R,5R)-1-((4-(4-(3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzithiepin-5-yl)phenoxy)methyl)phenyl)methyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride, Form I of 41x

[1470] (4R,5R)-27x (2.82 kg dry basis, 4.7 mol) was dissolved in MTBE (9.4 L). The solution of (4R,5R)-27x was passed through a 0.2 mm filter cartridge into the feeding vessel. The flask and was rinsed with MTBE (2 x 2.5 L). The obtained solution as passed through the cartridge filter and added to the solution of (4R,5R)-27x in the feeding vessel. DABCO (diazabicyclo[2.2.2]octane, 0.784 kg, 7.0 mol) was dissolved in MeOH (14.2 L). The DABCO solution was passed through the filter cartridge into the 100 L nitrogen-flushed reactor. The Pyrex bottle and the cartridge filter were rinsed with MeOH (7.5 L) and the solution was added to the reactor. The (4R,5R)-27x solution was added from the feeding vessel into the reactor at 37°C over a period of 10 min, while stirring. Methanol (6.5 L) was added to the Pyrex bottle and via the cartridge filter added to the feeding vessel to rinse the remaining (4R,5R)-27x into the reactor. The reaction mixture was brought to 50-60°C over 10-20 min and stirred at that temperature for about 1 h. The mixture was cooled to 20-25°C over a period of 1 h. To the reaction mixture, methyl t-butyl ether (MTBE) (42 L) was added over a period of 1 h and stirred for a minimum of 1 h at 20 - 25°C. The suspension was filtered through a Büchner funnel. The reactor and the filter cake were washed with MTBE (2 x 14 L). The solids were dried on a rotary evaporator in a 20 L flask at 400 – 12 mbar, 40°C, for 22 h. A white crystalline solid was obtained. The yield of 41x (Form I) was 3.08 kg (2.97 kg dry, 93.8 %) and the purity 99.7 area % (HPLC; Kromasil C 4, 250 x 4.6 mm column; 0.05% TFA in H₂O/0.05% TFA in ACN gradient, UV detection at 215 nm).

[1471] Example 1467a

[1472] Conversion of Form I of Compound 41x into Form II of Compound 41x.

[1473] To 10.0 grams of Form I of 41x in a 400 mL jacketed reactor is added 140 mL of MEK. The reactor is stirred (358 rpm) for 10 minutes at 23°C for 10 minutes and the stirring rate is then changed to 178 rpm. The suspension is heated to reflux over 1 hour using a programmed temperature ramp (0.95°C/minute) using batch temperature control (cascade mode). The delta T_{max} is set to 5°C. The mixture is held at reflux for 1 hour. The mixture is cooled to 25°C. After 3 hours at 25°C, a sample of the mixture is collected by filtration. Filtration is rapid (seconds) and the filtrate is clear and colorless. The white solid is dried in a vacuum oven (80°C, 25 in. Hg) to give a white solid. The remainder of the suspension is stirred at 25°C for 18 hours. The mixture is filtered and the cake starts to shrink as the mother liquor reaches the top of the cake. The filtration is stopped and the reactor is rinsed with 14 mL of MEK. The reactor stirrer speed is increased from 100 to 300 rpm to rinse the reactor. The rinse is added to the filter and the solid is dried with a rapid air flow for 5 minutes. The solid is dried in a vacuum oven at 25 in. Hg for 84 hours to give Form II of 41x.

[1474] All patents, publications, textbooks, articles and any other publications referenced in this application are incorporated herein by reference in their entirety for all purposes.